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Review Article

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The Gut Microbiome as a Biomarker for Tuberculosis Recurrence and Treatment Resistance: Addressing Gaps in Prognostic Tools

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ABSTRACT

Purpose and aim: Tuberculosis persists as a formidable global health challenge, characterized by high rates of post-treatment recurrence, relapse, and the emergence of multidrug-resistant strains, which remain inadequately predicted by conventional sputum-based, radiographic, and immunological biomarkers. This review critically evaluates current evidence on the gut microbiome as a prognostic biomarker for tuberculosis recurrence and treatment resistance.

Methods: A structured literature search was conducted in PubMed and Web of Science to identify English-language publications from 2010 onward, using combinations of the keywords tuberculosis, *Mycobacterium tuberculosis*, gut microbiota, gut-lung axis, recurrence, treatment resistance, drug resistance, and biomarkers. Peer-reviewed original research articles, clinical studies, and relevant review papers were included, while editorials, conference abstracts, case reports, duplicate publications, and studies not directly related to the review objectives were excluded.

Results and Conclusion: Evidence reviewed indicates that gut microbiome dysbiosis is consistently associated with tuberculosis treatment outcomes, including recurrence and treatment resistance. A reduced abundance of short-chain fatty acid-producing bacteria and an enrichment of opportunistic pathogens were frequently linked to impaired immune responses, disease progression, and poor therapeutic outcomes. Multi-omics studies suggest that combined microbial and metabolite signatures have greater prognostic potential than individual microbial taxa, although validation across diverse populations remains limited. Overall, the current evidence supports the gut microbiome as a promising source of non-invasive biomarkers for predicting tuberculosis outcomes while highlighting the need for standardized methodologies and large prospective clinical studies before routine clinical implementation.

What is "already known":	• Tuberculosis recurrence and treatment resistance remain major clinical problems • Current sputum-based, radiological, and immunological tools are limited in predicting long-term treatment outcomes. • The gut-lung axis can influence immune responses during TB treatment.
What this article adds:	• This review uses both human and animal evidence to link gut microbiome dysbiosis with TB progression, treatment response, recurrence, and drug resistance. • It highlights the potential prognostic value of microbiome-related changes, especially the loss of bacteria that produce short-chain fatty acids and the emergence of opportunistic taxa. • It discusses how microbiome-based biomarkers could complement, rather than replace, conventional TB diagnostic and monitoring tools. • It identifies the main barriers to clinical use, including methodological variation, dietary and geographical differences, confounding clinical factors, and the need for standardized multicenter validation studies.

1. Introduction

Tuberculosis (TB), caused primarily by *Mycobacterium tuberculosis* (MTB), remains one of the leading causes of death from a single infectious agent worldwide despite substantial advances in diagnosis, treatment, and public health interventions. According to the latest global estimates, approximately 10.7 million individuals developed TB in 2024, resulting in nearly 1.23 million deaths, including around 150,000 attributable to multidrug-resistant (MDR) TB. The global burden of TB continues to be amplified by socioeconomic inequalities, malnutrition, HIV co-infection, limited healthcare access, and the ongoing emergence of MDR and extensively drug-resistant (XDR) strains, particularly in high-burden settings (1-4). Collectively, these challenges continue to undermine global TB control efforts and underscore the need for improved strategies for disease prevention and management.

Among the unresolved challenges in TB control, disease recurrence remains particularly important because it reflects incomplete treatment success and contributes to continued transmission, increased healthcare costs, and the emergence of drug resistance. Reported recurrence rates range from approximately 5% to 20%, indicating that successful completion of chemotherapy does not necessarily guarantee long-term cure (2). Recurrent TB arises through two distinct mechanisms: relapse, resulting from reactivation of the original infecting strain due to the persistence of viable bacilli despite treatment, and exogenous reinfection, in which individuals acquire a genetically distinct MTB strain following successful treatment (5). While relapse generally occurs within the first months after treatment completion, reinfection may occur at any time in regions with ongoing community transmission. Differentiating these mechanisms is clinically important because they reflect different biological processes and require distinct public health strategies. More importantly, the ability to identify patients at increased risk of recurrence before clinical relapse develops would facilitate individualized follow-up, optimize treatment monitoring, reduce disease transmission, and improve resource allocation in TB-endemic regions (3, 5, 6).Current diagnostic and monitoring approaches, including sputum smear microscopy, mycobacterial culture, molecular assays such as Xpert MTB/RIF, tuberculin skin testing, and interferon-γ release assays (IGRAs), have substantially improved the diagnosis of active TB and the detection of rifampicin resistance, particularly in resource-limited settings (1, 7, 8). Nevertheless, these methods primarily assess the presence of MTB or host immune sensitization and provide limited information regarding future clinical outcomes. They cannot reliably predict treatment response, recurrence, progression from latent to active disease, or the subsequent emergence of drug resistance, underscoring the urgent need for robust prognostic biomarkers to support precision TB management (6, 8, 9). Consequently, there is growing interest in identifying reliable prognostic biomarkers that can predict disease recurrence before clinical

manifestations become evident. Earlier recognition of patients at high risk of relapse could improve post-treatment surveillance, optimize healthcare resource allocation, reduce transmission, and facilitate more personalized therapeutic interventions. Among emerging candidates, gut microbiome-derived biomarkers have attracted considerable attention for their potential to enable non-invasive risk stratification while providing mechanistic insights into host–microbe interact-tions that influence TB outcomes (3).

Growing evidence suggests that the gut microbiome may represent one such biomarker. Beyond its fundamental role in maintaining intestinal homeostasis, the gut microbiota functions as an essential regulator of systemic immunity through the gut-lung axis, a bidirectional communication network linking the gastrointestinal tract and the respiratory system (Figure 1). By producing microbial metabolites, particularly short-chain fatty acids (SCFAs), e.g., acetate, propionate, and butyrate, the gut microbiota influences the differentiation and function of dendritic cells, macrophages, regulatory T cells, and other immune populations that are critical for host defense against MTB. Anti-TB chemotherapy itself can profoundly disrupt gut microbial communities, leading to persistent dysbiosis that may impair immune homeostasis long after treatment completion. Such alterations have increasingly been implicated in treatment failure, persistent inflammation, recurrence, and the development of drug resistance, suggesting that microbiome composition may reflect both disease progression and therapeutic outcomes (10).

Recent microbiome studies have further strengthened this hypothesis by identifying microbial signatures associated with recurrent TB. For example, enrichment of *Pseudomonas* species has consistently been associated with treatment failure and recurrent disease. At the same time, an increased *Pseudomonas*-to-*Mycobacterium* ratio has been reported among patients with recurrent TB compared with those with primary infection, suggesting that alterations in the microbial ecosystem may create a pulmonary environment that favors disease recurrence (10, 11). Although these observations remain preliminary, they highlight the growing potential of microbiome-based biomarkers for predicting disease outcomes and guiding personalized therapeutic interventions.

This narrative mini-review aims to synthesize current evidence regarding the relationship between the gut microbiome, TB recurrence, and treatment resistance, with particular emphasis on the potential of microbiome-derived biomarkers to address existing prognostic limitations. We discuss the biological mechanisms linking gut microbial dysbiosis to anti-mycobacterial immunity, summarize recent clinical and experimental evidence, identify current knowledge gaps, and explore emerging analytical approaches, including machine learning and precision medicine, that may facilitate microbiome-guided risk stratification and individualized TB management. An overview of the evolution of microbiome research in TB is presented in Figure 2.

2. Method

To enhance the transparency of this narrative review, the literature was identified through structured searches of PubMed and Web of Science using combinations of keywords including: "tuberculosis", "*Mycobacterium tuberculosis*", "gut microbiota", "gut-lung axis", "recurrence", "treatment resistance", "drug resistance", and "biomarkers". The search primarily included peer-reviewed original research articles, clinical studies, and high-quality review papers published in English over the past 16 years, while landmark earlier publications were incorporated where necessary to provide historical context and support key concepts. The selected evidence was synthesized narratively to provide a comprehensive overview of current knowledge and emerging research directions in this field.

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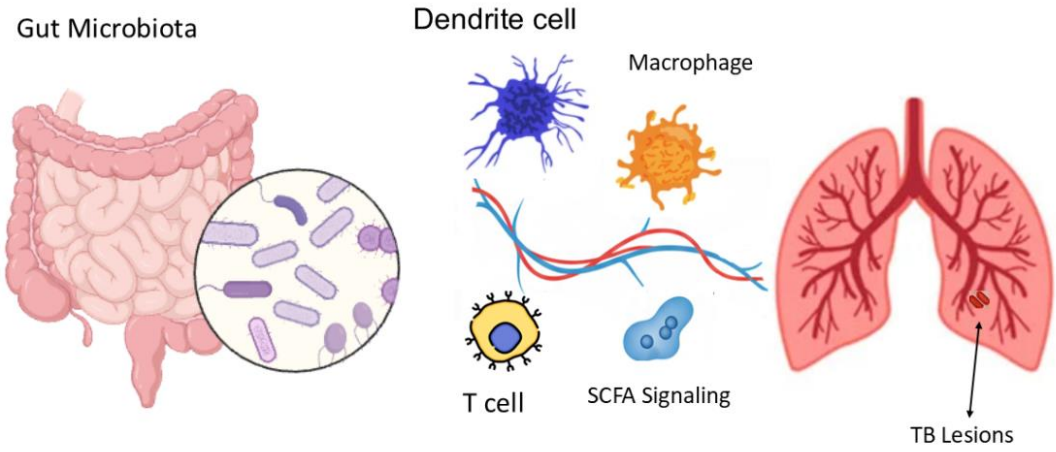

Figure 1. The two-way signalling between the gut microbiota and immune response during tuberculosis infection. Commensal gut bacteria (left part) produce short-chain fatty acids (acetate, propionate, and butyrate). In the pulmonary environment, short-chain fatty acids signalling modulates T cell differentiation and Dendritic cell function, shaping the adaptive immune response. This gut-lung axis affects the host's capacity to control MTB infection and reduce tuberculosis lesion formation (right part).

3. The Role of Gut Microbiome in Tuberculosis Pathogenesis

Recent studies have shown significant differences between a healthy person's gut and an individual with TB in both diversity and the balance of dominant bacterial phyla (12-15). Across multiple cohorts, healthy controls typically exhibit higher alpha diversity and a more abundant community of commensal taxa. In contrast, patients with active pulmonary TB tend to show a noticeable loss of microbial richness and evenness, with a shift in the relative abundance of *Bacteroidetes* and *Firmicutes* (Table 1) (13, 16). Furthermore, studies show that TB patients often have fewer beneficial *Firmicutes*, such as *Ruminococcaceae* and *Lachnospiraceae*, which are important butyrate-producing taxa. They also have lower levels of *Bifidobacterium* and *Lactobacillus*, which are usually more common in healthy people (Table 1) (16). In the meantime, an overrepresentation of certain *Bacteroidetes* and *Proteobacteria* is observed in active TB, contributing to a transformed *Bacteroidetes/Firmicutes* ratio that is repeatedly associated with dysbiosis and impaired immune regulation (17, 18). Multiple studies with large multi-cohort datasets from various regions can support the idea of a consistent pattern, despite differences in diet and geography; patients with TB repeatedly show the same microbial diversity and depletion of key bacteria that produce SCFAs (14).

These shifts in composition are observed not only in newly diagnosed patients but also persistently during and after treatment, suggesting that TB and its treatment disrupt gut microbiome community structure to the point that it may cause lasting consequences for host immunity and susceptibility to recurrence (19). The gut-lung connection is not a simple signal; it is an exact immunological calibration that, when disrupted, can cause TB to return. The primary mechanism involves impairment of adaptive immunity, with gut dysbiosis directly contributing to the host's ability to maintain an efficient lung defence (20). In particular, the loss of commensal bacteria can signal a reduction in the signal required to train T cells. Without these cues, the T-helper-1 (Th1) and T-helper-17 (Th17) lymphocyte populations, which are crucial for maintaining MTB, fail to expand or relocate efficiently to the infection site, contributing to a weakened granuloma structure that controls the bacteria (Table 1) (21).

Table 1. Key microbial taxa alterations in tuberculosis: dysbiosis patterns, functional consequences, and clinical impact.

Component/ Mechanism	Microbial Alteration	Functional Consequence	Impact on TB Control	Type of evidence	Ref
Microbial Composition	↓ Alpha diversity & richness	Dysbiosis, altered Bacteroidetes-to-Firmicutes ratio, loss of colonization resistance	Reduced short-chain fatty acid production	Human studies	(22)
	↓ Firmicutes (Ruminococcaceae, Lachnospiraceae)			Human studies	
	↓ *Bifidobacterium* & *Lactobacillus*			Human studies	
	↑ *Bacteroidetes* & *Proteobacteria*			Human studies	
Gut-Lung Axis Immunity	Loss of commensal signals	Impaired adaptive immunity	↓ T helper-1 & T helper-17 expansion/migration	Animal & human studies	(23)
	Reduced short-chain fatty acid	Defective T-cell training	Weakened granuloma structure	Animal & human studies	
Barrier Integrity	Increased permeability ('Leaky Gut')	Chronic low-grade systemic inflammation	Immune exhaustion T-cell dysfunction Impaired macrophage response	Animal & human studies	(23)
	Translocation of microbial products (LPS)			Mechanistic studies	
Drug Metabolism & Resistance	Enrichment of resistance genes	Altered drug exposure	Variable drug efficacy	Animal & human studies	(9)
	Xenobiotic transformation enzymes	Reservoir for resistance genes	Functional drug resistance	Mechanistic studies	

On the other hand, beyond cellular deficiencies, the physical integrity of the gut barrier can become a significant weakness. Gut dysbiosis often contributes to a "leaky" intestine, allowing microbial products to escape from the gut lumen into the bloodstream. This translocation can lead to chronic, low-grade systemic inflammation. While inflammation is typically a defense mechanism, this rapid, background noise can paradoxically tire the immune system, leading to T-cell dysfunction and impairing targeted macrophage responses needed to eliminate the pathogen (20, 24). Eventually, this immunological imbalance creates an opportunity for the pathogen. In patients with latent infection or those who have just finished an antibiotic course, the compromised immune defenses caused by persistent gut dysbiosis increase the chance that dormant bacilli will reactivate (25). This mechanical link helps explain the higher statistical susceptibility to relapse in patients with poor gut recovery, as their bodies lack the sustained immune control needed to prevent latent or dormant bacteria from becoming active again (25).

Extended anti-TB therapy further changes the gut and respiratory microbiota in ways that can damage immune control and favor treatment failure or recurrence. Standard first-line regimens combining isoniazid, rifampicin, pyrazinamide, and ethambutol, as well as more extended MDR-TB regimens, are linked with persistent exhaustion of beneficial *Firmicutes* taxa (notably Rumino-coccaceae and Lachnospiraceae) and Bifido-bacteriaceae, alongside expansion of *Bacteroidota* and opportunistic genera, sometimes months to years after treatment conclusion (23). These shifts reduce SCFA production and colonization

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resistance, weakening mucosal barrier integrity and synchronizing T cell and macrophage function, which are critical for sterilizing MTB infection (26). Even though SCFAs are often described as protective metabolites, their immune-logical effects should be interpreted in a context-dependent manner. Acetate, propionate, and butyrate could support epithelial barrier integrity, regulatory T-cell differentiation, and antiinflammatory signalling. However, their effects may vary according to concentration, tissue site, receptor expression, host metabolic status, and the stage of infection (23). SCFAs may suppress proinflammatory cytokine responses, such as interferon-gamma, interleukin 17, and macrophage-mediated responses, which are important for antimycobacterial immunity. So, reduced SCFA-producing taxa in TB should not be interpreted simply as a uniformly protective or harmful signal (27). Instead, SCFAs profiles may reflect a balance between immune regulation, antimicrobial defence, and excessive inflammation, and their prognostic value requires careful validation in longitudinal TB cohorts (23). Exceeding immune effects, microbial metabolism can directly influence anti-TB drugs and contribute to various drug exposures. Gut bacteria show diverse enzymes that transform xenobiotics. Experimental investigation in animal models shows that rifampicin-containing combinations can drive marked overgrowth of specific *Bacteroides* and Verrucomicrobiaceae while depleting *Clostridia*, changes that correlate with altered macrophage activation and reduced production of tumor necrosis factor α and interleukin-1 (IL-1) in the lung. Similarly, antibiotics enforce strong selection for genes with resistance within the microbiome (23). Prolonged studies on TB patients and mice demonstrate increased abundance and diversity of antimicrobial resistance determinants after isoniazid, rifampicin, pyrazinamide, and ethambutol or MDR-TB regimens, including overlapping genes with those conferring resistance to rifampicin and other broad-spectrum drugs (26). Although most of these factors reside in non-mycobacterial species, their presence raises concern about the microbiome, which can act as a reservoir and amplifier of resistance under constant antibiotic pressure (26). Antibiotic-induced dysbiosis also appears to alter host susceptibility to MTB and to modulate bacterial responses during and after treatment. In animal models such as mice, broad-spectrum or antibiotic-specific pre-treatment for TB reduces gut diversity, impairs mucosal-associated invariant T and TH17 responses, and increases pulmonary bacterial loads after aerosol challenge. This consequence can be partially mitigated by fecal microbiota trans-plantation (FMT) (23). HRZ-based regimens have been shown to affect reprogramming alveolar macrophages toward a less active phenotype, with reduced major histocompatibility complex class II (MHC II), tumor necrosis factor, and IL-1 production, and diminished ability to restrict intracellular bacilli, again linked to prior disruption of gut communities (23). Clinical studies in humans show that patients on treatment or recently cured frequently maintain a "post-antibiotic" micro-biome, characterized by loss of SCFA-producing commensals and an abundance of pathobionts such as *Pseudomonas* and *Enterococcus*, patterns linked to treatment failure, recurrent TB, and a greater risk of reinfection (17). Altogether, these studies suggest that microbiome disruption by anti-TB regimens not only shows collateral damage but may actively contribute to functional drug resistance and relapses by altering drug handling, immune competence, and ecological barriers to MTB resurgence (19).

4. Evidence from Clinical and Experimental Studies

The persistent gut dysbiosis during and after TB therapy has been reported not only in China and India but also in other high-burden regions such as Haiti and multiple African settings, strengthening the idea that microbiome changes are geographically restricted but reflect a typical host response to infection and intensive antibiotic exposure (28). These studies frequently describe long-term depletion of SCFA-producing taxa and *Bifidobacterium*, alongside enrichment of opportunistic genera such as Fusobacterium and Enterococcus during treatment, with only partial recovery even

more than a year after completion of therapy. In some cohorts, specific community structures and reduced microbial richness have been tentatively associated with higher risk of relapse or poor weight gain, suggesting that gut signatures could become part of recurrence-risk stratification in the future. Human data from MDR-TB cohorts further highlight the prognostic potential of microbiome profiling. Patients' prolonged and second-line regimens treatment showcase shifts in *Bacilliota*/*Bacteroidota* ratios and unique constellations of bacterial biomarkers during treatment and post-recovery. Some taxa remained significantly altered even after receiving treatment (10). Animal experiments further enhanced the mechanistic understanding of how antibiotic-induced dysbiosis exacerbates TB susceptibility and pathology. Mouse models of broad-spectrum antibiotic pre-treatment before MTB infection continuously show higher bacillary loads in lungs and extrapulmonary sites, accompanied by impaired Th1 responses, increased regulatory T cells, and reduced Interferon (IFN) and tumor necrosis factor (TNF) production (23). Remarkably, FMT from untreated or probiotic-supplemented donors can reverse these defects, normalize lung DC function, and partially restore resistance, underscoring a causal gut-lung axis in TB immunity (29). These animal data align with studies dissecting the impact of individual anti-TB drugs on gut communities. Regimens containing isoniazid and pyrazinamide, for example, have been linked to greater loss of commensals and more pronounced increases in TB burden than rifampicin alone in murine models, and this susceptibility can again be alleviated by reintroducing healthy microbiota via FMT. Such findings support the concept that microbiomepreserving or restoring strategies (targeted probiotics, synbiotics, or timed FMT) might reduce dissemination and improve bacterial clearance when used as adjuncts to standard chemotherapy (30). Multiomics integration and early machine learning models indicate that combining microbial taxa with specific metabolites improves discrimination between active TB, latent infection, and post-treatment states compared to the microbiome or metabolome alone. Some of these integrated signatures align with systemic traits such as low BMI, hypocholesterolemia, and micronutrient deficiencies, suggesting that gut-mediated metabolic disruption may be a critical mediator linking microbiome injury to poor clinical prognosis and delayed recovery. As datasets expand, these biomarkers, driven by omics, could support risk-adapted follow-up, selection of candidates for therapies targeting the microbiome, and potentially earlier detection of approaching relapse (31). However, converting this expanding body of evidence and database into robust clinical tools presents numerous challenges and multiple factors to consider. Studies conducted on humans can differ significantly in design, sequencing methods, sample handling, analytic pipelines, and definitions of TB phenotypes, making comparisons across cohorts difficult and limiting reproducibility. Many reports are affected negatively by small sample sizes and inadequate adjustment for major confounders such as diet, HIV status, diabetes, malnutrition, concurrent antibiotics, and local sanitation, all of which significantly influence microbiome structure (32). Geographic and cultural diversity contributes to further complexity because baseline microbiomes can differ across populations, in ways that a single taxon may perform and carry out different functions or have different prognostic implications in different diets or environments. The data gathered from the studies are primarily observational, so differentiating cause from consequence, whether dysbiosis directly drives treatment failure and recurrence or mirrors severe disease and heavy antibiotic use in the treatment process, remains difficult. Larger, multicenter longitudinal cohorts with standardized protocols, careful selection controls, and balanced multi-omics workflows from high-burden regions will be required to overcome these limitations (33). The progression of evidence supporting microbial shifts and their mechanistic interpretation is summarized in Figure 2, highlights the transition from descriptive microbiome profiling to functional and immune-integrated models of TB pathogenesis.

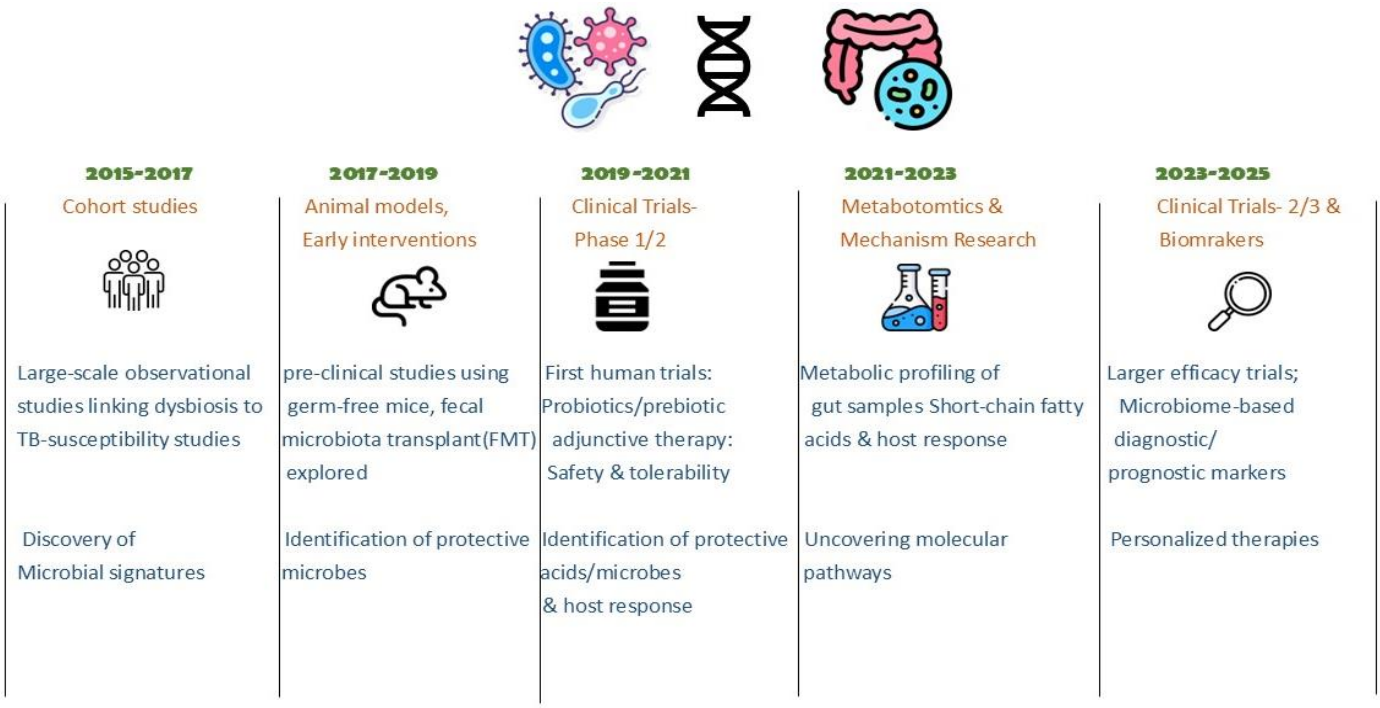

Figure 2. Timeline of representative studies on the gut microbiome in tuberculosis 2015-2025. The timeline shows key studies that evolved from simple microbiome profiling toward a better understanding of immune mechanisms, treatment response, biomarkers, and possible microbiome-based therapies.

Table 2. Representative human and animal studies on gut microbiome alterations in tuberculosis

Population/Model	Study Design	Key Findings	Clinical Significance	Ref.
46 pulmonary tuberculosis patients and 61 healthy controls (China)	Human	Reduced short-chain fatty acid-producing bacteria in tuberculosis; microbial signatures distinguished patients from controls.	Potential diagnostic biomarkers for active tuberculosis.	(12)
Active tuberculosis, latent tuberculosis infection, treated patients, and healthy controls (China)	Human	Anti- tuberculosis therapy decreased beneficial bacteria and increased *Bacteroides*.	Indicates treatment-induced gut microbiome alterations.	(34)
Newly diagnosed and recurrent tuberculosis patients (China)	Human	Recurrent tuberculosis showed greater microbial dysbiosis than newly diagnosed disease.	Associated with immune regulation and recurrence risk.	(5)
Patients during and after anti- tuberculosis treatment (Haiti)	Human	Persistent changes in gut microbiota persisted after treatment.	May contribute to delayed immune recovery and relapse.	(35)
Active tuberculosis, latent tuberculosis infection, and healthy controls (Taiwan)	Human	Differences in the *Firmicutes*-to-*Bacteroidetes* ratio among study groups.	Linked gut microbiota with host immune responses.	(36)
Mice treated with anti-tuberculosis drugs (USA)	Animal	Long-term therapy depleted beneficial bacterial genera.	Demonstrated persistent microbiome disruption after treatment.	(37)
Antibiotic-treated mice infected with *Mycobacterium tuberculosis* (India)	Animal	Gut microbiota depletion reduced beneficial bacteria and increased *Enterococcus*.	Suppressed protective immunity; FMT* restored immune function.	(38)

* FMT: fecal microbiota transplantation

5. Gaps and Opportunities in Gut Microbiome Research in Tuberculosis: Focus on Biomarkers

Recent studies have shown that the gut microbiome, the community of microbes residing in the digestive tract, influences TB outcomes, treatment response, and the risk of relapse. A lower diversity of gut microbes and fewer beneficial bacteria, such as *Bifidobacterium*, *Ruminococcus*, and other SCFA producers important for colon health, are linked with poor outcomes and more relapses. These shifts persist for months after treatment and are reported in TB hotspots such as China, India, and parts of Africa. Animal models demonstrate that gut imbalance represents an unhealthy shift in gut microbiome populations, which can increase MTB burden and alter immune responses in the lungs and other organs. Restoring gut microbiota with fecal FMT or probiotics, such as Lactobacillus plantarum and related strains, can help restore diversity, rebalance immunity, and lower bacterial load in experimental systems. These findings suggest that microbiome changes are not only biomarkers (measurable indicators) of disease but also potential therapeutic targets (39).

Studies using genomic tools and metabolomic methods have identified specific gut bacteria and metabolites associated with active TB, relapse risk, and different stages of recovery. Levels of fecal butyrate, valeric acid, and indole propionate are often lower in TB patients than in healthy individuals and may signal disease activity and higher relapse risk. Integrated genomic and metabolomic analyses indicate that TB-associated gut dysbiosis can reduce microbial capacity for vitamin synthesis and energy metabolism, potentially worsening immune dysfunction and nutritional deficits. Integrative machine-learning models that combine microbial profiles with metabolite features have successfully distinguished active, latent, and post-treatment TB in research cohorts, underscoring the potential for robust clinical biomarker development. However, geographical variation, dietary patterns, malnutrition, and comorbidities (especially HIV) still limit the generalizability of proposed signatures. In summary, microbial and metabolite biomarkers, together with microbiome profiles, offer promising tools for monitoring treatment, predicting relapse, and guiding targeted interventions. However, multicenter studies with standardized methods, longer follow-up, and diverse populations are needed before routine clinical application is feasible (40, 41). Dealing with gut issues formed from long-term TB treatment is not easy to overlook; it is a real game-changer for how well patients actually recover. That is why newer approaches, such as carefully selected probiotics and prebiotics, are getting so much attention. They work in various ways: by churning out natural antimicrobials, physically blocking harmful bugs from settling in, and helping the immune system. All of this could go a long way toward mitigating the side effects that TB drugs have on our gut bacteria (42). Looking ahead, there is significant potential in using plant-based probiotics. They are not only sustainable and easier to access, but they also play well with a wide range of foods and offer additional benefits, such as boosting antioxidant defenses. Also, these plant-powered options could be budget-friendly, especially in places where TB skyrockets and resources are scarce. But the catch is, we really need solid clinical studies to support their use and demonstrate that they actually make a difference in TB care (43). In Table 3, microbiome-based biomarkers are compared to conventional TB prognostic tools.

6. Barriers to the Clinical Implementation of Microbiome-Based Tools

Despite the potential of microbiome signatures as prognostic indicators, several challenges remain in transitioning from research to practical clinical use. These obstacles affect every stage of the process, from the moment patient sampling begins through to data analysis (9).

6.1. Methodological Heterogeneity

One major issue is the sheer inconsistency across studies. Researchers tend to use different sequencing platforms and DNA extraction kits, and to focus on different hypervariable regions when analyzing 16S rRNA data. These choices, under-covered as technical choices, can actually twist results, bias towards certain bacterial types over others, and make it difficult to discover reliable, universal biomarkers that hold up across different labs and studies (27, 44).

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Table 3. Comparison of microbiome-based biomarkers and conventional prognostic tools for TB[§]: current evidence, clinical utility, and translational potential

Feature	Microbiome-based biomarkers (TB-specific evidence)	Conventional TB prognostic tools	References
Sensitivity	Moderate to high; gut/lung microbial shifts distinguish active TB, LTBI[†], and healthy controls.	Variable; sputum smear low sensitivity, GeneXpert higher sensitivity	(45, 46)
Specificity	Moderate; TB-associated dysbiosis patterns (e.g., ↓ *Faecalibacterium*, ↑ *Streptococcus*) but overlap with other inflammatory states.	High for molecular assays (GeneXpert MTB/RIF[‡]), but limited for clinical markers	(45, 46)
Prognostic value	Can differentiate LTBI → active TB transition via microbial diversity loss and immune-linked taxa changes	Limited; mainly reflects current infection status, not progression risk	(45)
Turnaround time	Relatively slow (sequencing, bioinformatics pipeline required)	Rapid for molecular tests (e.g., GeneXpert ~2 hours)	(46)
Cost	Higher (16S/shotgun sequencing required; still research-level in TB context)	Lower for smear microscopy; moderate for molecular diagnostics	(46)
Stability of markers	Moderate stability; microbiome reflects long-term immune/metabolic state but is influenced by antibiotics and diet	High short-term reliability; reflects current bacterial burden	(45, 47)
Clinical implementation stage	Experimental / research-based (no standardized clinical microbiome TB test yet)	Fully implemented (WHO-recommended diagnostic algorithms)	(47)
Personalization potential	High; may stratify patients by immune–microbiome phenotype and predict treatment response.	Low to moderate; mostly standardized treatment pathways	(43)

§ TB: Tuberculosis
† LTB: Latent tuberculosis
‡RIF: Rifampicin

6.2. Host and Environmental Confounders

The human microbiome is actually really personal and highly responsive to our environment. Factors like diet, age, body mass, sex, and even where a person lives can all alter the microbial landscape. On top of that, conditions that are common in TB endemic areas, such as HIV, diabetes, and malnutrition, can make their own special microbial disruptions, which can very easily mask the signals researchers are trying to find (48, 49).

6.3. Technical and Bioinformatics Hurdles

Working with clinical samples like blood or bronchoalveolar lavage fluid can be hard, too. These samples are often dominated by host DNA, sometimes up to 99%, which forces researchers to use complex techniques just to get enough microbial material to sequence. Then comes the analysis, where a lack of standardized bioinformatics tools and incomplete reference databases leaves a large amount of microbial "dark matter" unidentifiable (50, 51).

6.4. Standardization of Procedures

Perhaps the most practical complexity is the lack of global protocols for collecting, storing, and processing samples. While freezing at -80°C is considered the standard, it is often impractical and unrealistic in low-resource settings where TB is most prevalent. Furthermore, while chemical preservatives like RNA later can offer a more practical alternative, they can slightly alter the balance of species in a sample, introducing yet another variable (44, 52).

7. FUTURE DIRECTIONS

Advancing gut microbiome research in TB toward clinical applicability requires a cautious, stepwise, and evidence-driven translational framework. While current findings provide strong associative and mechanistic insights, most microbiome-based biomarkers and interventions remain in the exploratory stage, and their clinical utility has yet to be validated in well-designed prospective studies. A critical priority is the implementation of large-scale, prospective, multicenter longitudinal cohort studies across geographically, ethnically, and socioeconomically diverse TB-endemic regions, including Asia, Africa, and Latin America. Such studies are essential to evaluate the reproducibility and generalizability of microbiome signatures associated with disease progression, treatment response, and recurrence (53, 54). Standardization of study design, including biospecimen collection, storage conditions, sequencing platforms, and bioinformatics pipelines, will be necessary to reduce inter-study variability and improve comparability across cohorts (44, 55). In parallel, integrative multiomics approaches combining microbiome, metabolomic, transcriptomic, and host genetic data may provide a more comprehensive understanding of host-microbe interactions in TB. However, predictive machine learning models should be interpreted with caution, and their clinical relevance must be confirmed through external validation in independent cohorts. Emphasis should be placed on transparent, explainable models and rigorous statistical validation to avoid overfitting and ensure biological interpretability (56-58). Mechanistic studies using experimental models such as gnotobiotic systems and organ-on-chip platforms remain important for elucidating causal relationships within the gut–lung axis (46). Nevertheless, findings from these models should be carefully translated to human disease contexts, given inherent biological differences and limitations in recapitulating complex host environments. From a translational perspective, microbiome-based biomarkers and diagnostic tools, including sequencing-based assays or metabolite profiling, are promising but require rigorous validation before integration into routine clinical practice. Future research should therefore prioritize well-powered prospective validation studies and multicenter clinical trials designed to assess feasibility, reproducibility, and clinical impact in real-world settings (45, 59).

Finally, future progress in this field will depend on interdisciplinary collaboration among microbiologists, clinicians, bioinformaticians, and public health experts to ensure that microbiome research advances from associative findings to clinically validated applications that meaningfully contribute to TB control strategies (46, 47).

8. CONCLUSION

This review portrays the potential of the gut microbiome in TB research. What we are observing so far is interesting: changes in gut bacterial makeup, particularly a drop in bacteria that produce SCFAs and signs of dysbiosis that stick around during treatment, seem to correlate with how well patients respond to therapy, their risk of relapse, and even drug resistance. This raises real hope that markers based on the microbiome might one day provide insights that tools used today, such as sputum tests, imaging, or immune assays, cannot fully provide.

Rather than replacing conventional diagnostic methods, microbiome-based biomarkers are expected to complement existing clinical tools by improving risk assessment and supporting personalized TB management. Early identification of patients at higher risk of relapse or treatment failure may facilitate timely intervention and improve treatment outcomes.

At the same time, we are not yet at the final destination for everyday clinical practice. Most studies published are observational, and the field is rife with variability: different populations, diets, lab techniques, and data analysis methods make it even harder to pinpoint a consistent microbial marker that is reliable for predicting TB outcomes. So, for now, these biomarkers are best seen as a complement to standard tools rather than a replacement for them.

For future advancements, we require large, multicenter studies with patient follow-up, consistent sampling, aligned lab methods, and defined outcomes tracking (such as relapse, reinfection, treatment failure, and drug resistance). It is also important to connect different aspects, such as gut microbiome data, immune responses, metabolic profiles, and routine clinical data. This kind of approach can really improve the robustness of the broader picture for

higher-risk patients. So yes, there is real potential for microbiome-based treatment to be used in personalized TB care in the future. However, we have to be realistic: this transition cannot be rushed. Before any of the new strategies becomes practical, it needs to be tested and confirmed in real-world regions. The potential is real, but it has to be proven.

Future research should prioritize large, multicenter longitudinal studies with standardized microbiome sampling, harmonized analytical pipelines, and validation across diverse populations. Integrating microbiome profiles with host immune, metabolic, and clinical data through multi-omics approaches may facilitate the development of robust prognostic models suitable for clinical practice. Although several microbiome-targeted interventions have shown encouraging results in experimental settings, their clinical efficacy and long-term safety require confirmation in well-designed randomized controlled trials before routine implementation. Overall, microbiome-informed prognostic strategies have the potential to complement existing TB management by supporting precision medicine approaches and improving patient outcomes.

9. Declarations

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9.2. Conflict of interest

There are no competing interests between the authors.

9.3. Ethics

9.3.1. Consent to Participate declaration

This study is a mini review and was conducted using data from other studies, without including any human or animal samples.

9.3.2. Clinical Trial Number

Not applicable

9.3.3. Human Ethics &Consent to Participate declarations

Not applicable

9.4. Author Contributions Statement

MA: Writing Original Draft, Methodology, Review & Editing, **HGh:** Writing Original Draft, Methodology, Review & Editing, **BTM**: Writing Original Draft, Methodology, Review & Editing, **MN**: Writing Original Draft, Methodology, Review & Editing, **MoMa** & **AFH**: Writing Original Draft, Review & Editing, **MaMe**: Conceptualization, Methodology, Validation, Investigation, Resources, Writing Original Draft, Writing Review & Editing, Visualization, Supervision, Project administration, **SDS**: Conceptualization, Methodology, Validation, Investigation, Resources, Writing Original Draft, Writing Review & Editing, Visualization, Supervision, Project administration.

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