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REVIEW ARTICLE

The role of antimicrobial stewardship in the management of tuberculosis

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ABSTRACT

Antimicrobial stewardship (AMS) aims to optimize antimicrobial use, improve outcomes, and limit resistance. Tuberculosis (TB), causing 10.8 million cases and 1.25 million deaths in 2023, contributes substantially to the global resistance burden but has rarely been integrated into AMS initiatives. This review evaluates how AMS principles apply to TB care. Key differences include long standardized combination regimens, predominance of outpatient management, and the central role of adherence, which limit conventional AMS approaches such as empiric therapy or treatment shortening. Diagnostic stewardship, rapid drug susceptibility testing, therapeutic drug monitoring, and outcome documentation are critical to prevent treatment failure and emerging resistance. We conclude that explicit integration of TB into national AMS strategies is essential to preserve the efficacy of existing and novel TB drugs and improve patient outcomes.

Keywords: Tuberculosis. Antimicrobial stewardship. Drug-resistant tuberculosis. Diagnostic stewardship. Treatment monitoring.

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INTRODUCTION

Tuberculosis (TB) caused an estimated 10.8 million cases and 1.25 million deaths in 2023 and is the leading cause of death from a single infectious agent worldwide[1]. Drug-resistant TB compromises treatment outcomes, places a heavy burden on health-care systems, and represents a major obstacle to achieving the targets of the World Health Organization's (WHO) End TB Strategy[2].

Because the development of new compounds for TB treatment is slow and resource-intensive, repurposed antibiotics such as fluorquinolones, linezolid, carbapenems, and clofazimine have become essential components of regimens for drug-resistant disease[3]. Only in recent years have drugs such as bedaquiline, delamanid, and pretomanid been developed specifically for TB and now form the backbone of the short, all-oral regimens recommended by the WHO for the treatment of multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB)[4,5]. Until recently, treatment of MDR/RR-TB required up to 18 months of multidrug combinations, with cure achieved in fewer than 70% of patients[1]. The advent of bedaquiline-containing regimens has now enabled treatment durations of 6-9 months with cure rates approaching 90%, comparable to those for drug-susceptible TB. Reports of emerging resistance to bedaquiline are therefore of particular concern, as they threaten to undermine these therapeutic advances[6-8].

In this context, antimicrobial stewardship (AMS) plays an important role in preserving the effectiveness of both existing and newly developed drugs[9]. By promoting the rational use of antimicrobials, AMS seeks to improve patient outcomes while reducing toxicity, costs, and the emergence of antimicrobial resistance (AMR). In recent years, AMS programs have been implemented globally in response to the increasing threat of AMR. However, TB has rarely been explicitly included in these initiatives, despite accounting for a substantial proportion of the global AMR burden[10]. This review summarizes the current state of AMS in TB and outlines practical pathways and future directions for embedding AMS across the continuum of TB care.

Interplay between TB and other bacterial infections

The interplay between TB treatment and the management of other bacterial infections illustrates the broader challenges of AMR. Fluoroquinolones are widely used for the treatment of common bacterial infections and, at the same time, represent a crucial component of therapy for MDR/RR-TB. Prior treatment with fluoroquinolones – for example, in patients with suspected pneumonia – has been associated with diagnostic and therapeutic delays in pulmonary TB and with an increased risk of fluoroquinolone-resistant *Mycobacterium tuberculosis*[11-13].

Conversely, extensive evidence shows that the use of fluoroquinolones, linezolid, and rifampicin promotes the emergence of AMR in bacterial species other than *M. tuberculosis*[14-16]. It is therefore reasonable to assume that the use of these agents in TB treatment may likewise contribute to rising AMR rates among other bacterial pathogens. These multifaceted, bidirectional interactions between TB treatment and the management of other suspected or confirmed bacterial infections highlight that AMS must always be implemented across diseases and bacterial species boundaries, with TB care forming an integral component of such efforts.

DIFFERENCES BETWEEN AMS IN TB AND CONVENTIONAL AMS

The relative underemphasis of AMS for TB can be partly explained by structural and clinical features that distinguish TB care from other infectious diseases (Table 1).

Historically, TB has been managed through vertical program structures – stand-alone, disease-specific national prevention and care programs with standardized protocols that operate largely outside broader health-system and AMS frameworks. This organizational separation has limited integration with wider AMS policies and practices, which are typically managed at the clinical level by AMS teams[17]. Moreover, while most AMS activities are concentrated in the hospital setting, TB care is predominantly delivered in outpatient and community settings, creating an additional challenge for alignment with conventional AMS approaches.

Treatment strategies further underscore the differences between TB and conventional AMS. TB regimens are long, highly standardized, and pathogen-specific, leaving little scope for individualized stewardship strategies. In TB, microbiological confirmation is usually sought before starting therapy, whereas in many other infections, empiric broad-spectrum treatment followed by de-escalation is frequent.

Likewise, while conventional AMS emphasizes shortening treatment duration, for example, by self-directed antibiotic reassessments by prescribing clinicians, TB management is bound to standardized, prolonged regimens[18-20]. Combination therapy is mandatory in TB to prevent AMR, whereas monotherapy is preferred whenever possible in most other bacterial infections. Institution-specific guidelines for the management of common infections are often developed to take into account local cumulative antibiograms guiding empiric antimicrobial choices for common infections, whereas in TB, local resistance patterns play a lesser role since empiric therapy is limited and standardized regimens dominate[17,21-23].

Similarly, the transition from intravenous to oral therapy – a common AMS intervention in hospitals – is of limited relevance in TB, as initial intravenous treatment is reserved for selected patients with gastrointestinal absorption problems or those critically ill in intensive care[24-26].

Among AMS principles, treatment monitoring and outcome documentation play an exceptionally central role in TB, as they are critical to detecting inadequate response and preventing AMR. This requires a combined assessment of clinical symptoms, weight gain, chest imaging, and microbiological results, with sputum culture as the reference standard. Molecular assays such as Xpert® MTB/Rif (Cepheid, Sunnyvale, CA) are widely

Table 1. Key differences and shared principles between conventional AMS and TB-specific stewardship

Domain	Conventional AMS	AMS in tuberculosis
Organization	Local AMS teams with facility-specific protocols	Vertical national TB programs with standardized protocols
Setting	Predominantly hospital-based	Predominantly outpatient/community-based
Diagnostic approach	Empiric broad-spectrum therapy, de-escalation	Microbiological confirmation is usually required before treatment
Access and equity	Access to antimicrobials is generally less problematic	Equitable access, affordability, and avoiding stock-outs are critical for treatment continuity
Therapy type	Monotherapy is preferred when possible	Always use combination therapy to prevent resistance
Treatment duration	Typically short	Long, standardized regimens
Treatment monitoring	Focus on duration, IV-to-oral switch, and spectrum reduction	Regular clinical, microbiological, radiological monitoring; standardized outcomes; TDM
Outcome documentation	Variable, often limited	Standardized and essential for evaluation
Role of resistance epidemiology	Protocols adapted to local resistance patterns	Local resistance plays a minor role in empiric treatment choices; standardized regimens dominate
Preventive treatment	Mainly perioperative or selected high-risk groups	Preventive therapy of TB infection in high-risk individuals and close contacts
Route of administration	IV-to-oral switch central	Oral regimens are standard; IV is only rarely used
Adherence	Shorter regimens ease adherence; education mainly targets prescribers	Long treatment requires strict adherence; interruptions risk resistance/failure; structured education, counsel-ing, and support are essential
Stewardship objectives	Limit unnecessary broad-spectrum use to reduce selection pressure	Prevent resistance through adherence, appropriate regimens, and dosing

AMS: antimicrobial stewardship; TB: tuberculosis; IV: intravenous; TDM: therapeutic drug monitoring.

available and provide rapid information for initial diagnosis, but they are not suitable for treatment monitoring, as they cannot distinguish between viable and non-viable bacilli and may remain positive long after effective therapy has been initiated. For monitoring purposes of pulmonary TB, sputum culture remains the reference standard, whereas novel host- or pathogen-derived biomarkers are under clinical evaluation and may provide more accurate and timely measures of treatment response in the future[27-29]. Where available, therapeutic drug monitoring (TDM) may offer additional value by identifying malabsorption or subtherapeutic exposure in patients with poor response[30-32]. Standardized documentation of outcomes further ensures comparability, supports surveillance of resistance, and enables evaluation of AMS interventions. Beyond cure, completion, and failure, outcome reporting should capture adverse events, treatment modifications, and loss to follow-up. Embedding such data in registries strengthens accountability and aligns TB care with broader AMS principles.

Finally, patient adherence plays an exceptionally central role in TB stewardship. Successful outcomes depend on uninterrupted adherence to therapy over many months, as treatment interruptions risk AMR development and failure. By contrast, in conventional AMS, shorter treatment courses not only suffice but also reduce adherence challenges.

POTENTIAL ROLE OF AMS IN TB

Key AMS strategies in TB care are, among other interventions, designed to optimize the use of anti-TB drugs and limit the development and transmission of drug-resistant *M. tuberculosis* (Fig. 1). Previously, five specific measures for TB stewardship have been proposed, namely: (i) systematic exclusion of TB disease in candidates for preventive treatment; (ii) avoidance of molecular tests for microbiological monitoring in patients receiving treatment for TB disease; (iii) refraining from the unnecessary addition of drugs to standard regimens for drug-susceptible TB and avoiding the addition of a single drug to a failing regimen; (iv) substitution of rifampicin with appropriate drug-resistant TB regimens in cases of rifampicin mono-resistance, drug–drug interactions, or intolerance; and (v) routine assessment of malnutrition at baseline with monitoring of weight gain as a proxy for treatment response[10]. We previously defined ten clinical standards for AMS in TB through a structured Delphi process involving an international panel of TB and AMS experts to reach expert consensus[33]. These include: (1) integration of TB into national AMR action plans; (2) implementation of TB surveillance systems; (3) education of healthcare providers, individuals affected by TB, and the public; (4) integration of TB into AMS activities; (5) establishment of expert consultation services; (6) targeted testing and preventive treatment for individuals at risk for TB; (7) access to timely and comprehensive drug susceptibility testing (DST); (8)

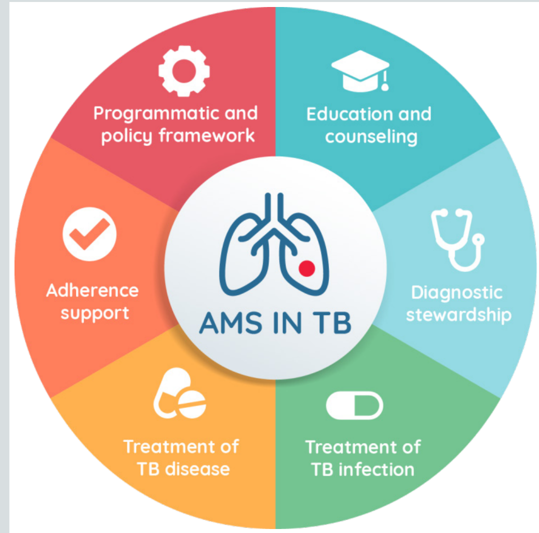

Figure 1. Key AMS strategies in TB. AMS: antimicrobial stewardship; TB: tuberculosis.

prioritization of efficacy, safety, and resistance prevention in TB treatment regimens; (9) clinical and microbiological monitoring of treatment response; and (10) assessment of adherence, drug exposure, and resistance in treatment failure.

PROGRAMMATIC AND POLICY FRAMEWORK

Programmatic and policy measures form the foundation of AMS in TB. Integration of TB into national AMR action plans ensures that stewardship principles are applied not only at the patient level but also across health systems. Strong surveillance systems are essential to capture epidemiological trends, monitor AMR, and provide the evidence base for adapting guidelines. Embedding TB within broader AMS activities also facilitates cross-learning between TB programs and stewardship structures established for other infectious diseases. This requires alignment between vertical TB programs and horizontal health system approaches, with clear responsibilities, resource allocation, and accountability. Ultimately, programmatic and policy frameworks create the structural conditions under which diagnostic stewardship, rational regimen design, and adherence support can be successfully implemented.

EDUCATION AND COUNSELING

Educational interventions and counseling are cornerstones of AMS and have been shown to be effective in improving antibiotic prescription behavior[17,34,35]. Such interventions are vital to maintaining knowledge of up-to-date practices and guidelines for antimicrobial use, while also enhancing awareness of local, regional, and global threats from AMR. This is equally true for TB, where ongoing clinical education is essential to ensure optimal patient care and appropriate prescribing practices, particularly in complex drug-resistant TB cases. In addition, multidisciplinary consultation services, such as expert treatment boards and consilium structures, further support individualized therapy and promote adherence to best practices, especially where local expertise is limited[36-40].

DIAGNOSTIC STEWARDSHIP

Diagnostic stewardship is a fundamental component of AMS, aiming to ensure that diagnostic tools are used effectively to guide optimal patient care and limit the emergence of AMR[41]. It includes the crucial pre-diagnostic steps of ensuring that the right patients are identified, appropriate clinical suspicion is established, and correct specimens are submitted for the appropriate investigations. This is particularly important in TB care, where a wide range of diagnostic tests is available and their proper use and interpretation critically depend on clinical judgment[42]. In addition to diagnosing TB disease, rapid and comprehensive DST remains essential to guide individualized therapy and prevent amplification of AMR. Phenotypic DST continues to serve as the reference standard but is limited by its long turnaround time. Near point-of-care assays such as Xpert® MTB/RIF Ultra and Xpert® MTB/XDR provide more rapid resistance information, though only for a restricted set of drugs. In contrast, next-generation sequencing (targeted next-generation sequencing [tNGS], whole genome sequencing [WGS]) enables faster and more comprehensive detection of resistance across all relevant agents, including bedaquiline, linezolid, and nitroimidazoles[43-45]. With the increasing adoption of tNGS and WGS in clinical practice worldwide, the translation of complex genomic findings into clear therapeutic decisions has become an integral component of stewardship. Standardized interpretation, adequate laboratory capacity, and affordability, therefore, remain critical, while timely and equitable access to high-quality diagnostics must be regarded as a core stewardship priority.

TREATMENT OF TB INFECTION

The clinical course of TB also differs markedly from most other bacterial infections. TB is characterized by distinct states of infection and disease. TB infection is defined as a persistent immune response to *M. tuberculosis* antigens without clinical, radiological, or microbiological indication of TB disease. It may persist silently for years but can progress to TB disease, a risk that can be substantially reduced through preventive treatment[46]. This approach is unique, since in most other bacterial infections, prophylaxis is generally restricted to perioperative settings or selected high-risk groups. In contrast, TB disease has traditionally been defined by overt clinical manifestations and characteristic organ pathology, which may or may not be accompanied by infectiousness. This duality creates a stewardship dilemma. On one hand, undetected or untreated TB infection may progress to TB disease, sustaining transmission and fueling AMR[47]. On the other hand, widespread preventive treatment of individuals with low risk of progression can result in overtreatment and unnecessary antimicrobial exposure, with attendant toxicity and contribution to AMR.

TREATMENT OF TB DISEASE

Within the broader framework of AMS, treatment stewardship in TB should focus on optimizing the management of TB disease through the selection of effective regimens, monitoring of treatment response, and avoidance and management of drug toxicity. Ineffective regimens remain the main driver of treatment failure and the development of AMR, underscoring the importance of evidence-based regimen design. Structured monitoring of clinical, microbiological, and radiological outcomes helps detect early signs of treatment failure and emerging AMR. Antibiotic dose optimization is a key AMS strategy aimed at improving treatment outcomes while reducing adverse effects and limiting the development of AMR[48]. This principle is particularly relevant in TB, where long treatment durations and the use of multiple drugs increase the risk of both toxicity and suboptimal exposure. TDM, where available, can further support dose optimization by identifying inadequate drug levels caused by malabsorption, drug–drug interactions, or individual pharmacokinetic variability, and by guiding timely dose adjustments[30]. Equally important are health system factors such as uninterrupted drug availability, avoidance of stock-outs, and financial accessibility, which are critical to ensure delivery of effective regimens and prevent resistance amplification[49,50]. Treatment monitoring is another essential pillar of AMS in TB, as early identification of inadequate response is crucial to prevent treatment failure and the emergence of AMR[28]. Existing tools include clinical evaluation, weight gain, chest imaging, and sputum culture, which remains the reference standard for assessing bacteriological conversion. However, culture is slow and resource-intensive, and molecular assays such as Xpert® MTB/RIF cannot distinguish between viable and non-viable bacilli, limiting their utility for monitoring. Novel approaches are therefore under evaluation, including molecular bacterial load assays, host- and pathogen-derived biomarkers, and transcriptomic signatures that may provide earlier and more accurate indicators of treatment response[29,51]. Incorporating such tools into routine care could enable more individualized regimen adjustments, prevent unnecessary prolongation of therapy, and facilitate earlier recognition of failing regimens, thereby strengthening AMR prevention and improving patient outcomes.

Delabeling of spurious antibiotic allergies is an important AMS measure[52,53]. Many patients carry allergy labels, particularly to β-lactams, that do not represent true hypersensitivity. Such labels restrict the use of first-line therapies, promote unnecessary broad-spectrum coverage, and increase reliance on less effective or more toxic alternatives. Structured history-taking, targeted skin testing, and supervised drug challenges can safely remove false labels, thereby optimizing therapy and reducing selective pressure for AMR. While adverse drug reactions to TB medications are common, true hypersensitivity reactions occur in only a minority of patients[54,55]. Nevertheless, they can severely compromise adherence and lead to treatment interruptions, which is an established risk factor for the development of AMR[56]. Moreover, unnecessary exclusion of first-line drugs based on unverified allergy labels may increase toxicity and jeopardize treatment outcomes. Although severe IgE- or T-cell-mediated reactions to anti-TB drugs are rare, skin tests, patch tests, and *in vitro* diagnostics to confirm or exclude true allergy are not well evaluated, resource-intensive, and not widely available[57]. Pragmatic delabeling strategies, including careful history-taking, risk stratification, and structured drug re-challenge, could help to avoid inappropriate labeling, ensure timely reintroduction of essential drugs, and support treatment adherence. Building standardized definitions, assessment frameworks, and multicenter evidence is therefore critical to embed delabeling practices into AMS and to strengthen AMR prevention and patient care.

Frequent interruptions in TB treatment due to drug shortages remain a major threat to successful treatment outcomes and the prevention of AMR[49]. These interruptions, often caused by procurement delays or disruptions of supply chains, lead to treatment interruptions and regimen modifications that jeopardize both individual and public health. Preventing shortages, therefore, requires political commitment and coordinated action across local, national, and global levels, ensuring uninterrupted access to quality-assured TB medicines.

Moreover, the management of adverse effects represents a unique challenge in TB compared with conventional antimicrobial therapy. Drugs such as linezolid, while highly effective, are associated with hematologic and neurologic toxicities that often necessitate dose adjustments or treatment interruptions[58]. These measures, though intended to improve tolerability, may inadvertently promote the emergence of resistance if drug exposure becomes subtherapeutic. Optimizing the balance between efficacy and safety, therefore, requires close clinical monitoring, TDM where available, and clear guidance on dose modification and toxicity management.

ADHERENCE SUPPORT

Adherence support constitutes a cornerstone of AMS in TB, as treatment success ultimately depends on uninterrupted and sustained treatment intake. The long treatment duration creates major challenges for patients, particularly when combined with frequent and sometimes severe adverse drug reactions. Additional barriers arise from the direct and indirect costs of treatment, including expenses for medications, transport, and repeated clinic visits, which may impose a substantial financial burden on patients and their families[50]. Non-adherence, whether due to toxicity, financial hardship, or social factors, is a major driver of treatment failure and the emergence of drug-resistant TB, thereby undermining both individual and public health outcomes. Addressing these obstacles requires a multipronged approach that combines patient-centered counseling, treatment literacy, and psychosocial as well as financial support at the individual and community level[56]. Digital adherence technologies offer additional tools to strengthen continuity of care, particularly in decentralized or resource-limited settings[59]. The use of fixed-dose combinations, which combine several drugs into a single tablet, has been instrumental in reducing pill burden and improving adherence[60]. Widespread implementation of fixed-dose combinations in first-line and selected second-line regimens is therefore another cornerstone of TB stewardship efforts.

CONCLUSION

AMS provides a vital framework to preserve the effectiveness of antimicrobial agents and to reduce the development and spread of AMR. Although important differences in the management of TB compared with other bacterial infections must be acknowledged, several established AMS strategies, such as clinical education and consultation, diagnostic stewardship, rational regimen design, dose optimization, and the avoidance and management of drug toxicity, are also applicable to TB. Integrating TB more explicitly into broader AMS programs will be crucial to improving patient outcomes and protecting the efficacy of both existing and novel anti-TB drugs in the future.

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CONFLICTS OF INTEREST

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ETHICAL CONSIDERATIONS

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

REFERENCES

1. World Health Organization. Global Tuberculosis Report 2024. Geneva: World Health Organization; 2024.
2. Available from: https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy
3. Dheda K, Mirzayev F, Cirillo DM, Udwadia Z, Dooley KE, Chang KC, et al. Multidrug-resistant tuberculosis. Nat Rev Dis Primers. 2024;10:22.
4. World Health Organization. WHO Consolidated Guidelines on Tuberculosis. Module 4: Treatment and Care. Geneva, Switzerland: World Health Organization; 2025.
5. Dheda K, Lange C. Towards shorter, safer, flexible, and more effective treatment regimens for drug-resistant tuberculosis. Lancet Respir Med. 2024;12:939-41.
6. Chesov E, Chesov D, Maurer FP, 0 I, et al. Emergence of bedaquiline resistance in a high tuberculosis burden country. Eur Respir J. 2022;59:2100621.
7. Derendinger B, Dippenaar A, de Vos M, Huo S, Alberts R, Tadokera R, et al. Bedaquiline resistance in patients with drug-resistant tuberculosis in Cape Town, South Africa: a retrospective longitudinal cohort study. Lancet Microbe. 2023;4:e972-e82.
8. Günther G, Mhuulu L, Diergaardt A, Dreyer V, Moses M, Anyolo K, et al. Bedaquiline resistance after effective treatment of multidrug-resistant tuberculosis, Namibia. Emerg Infect Dis. 2024;30:568-71.
9. Dyar OJ, Huttner B, Schouten J, Pulcini C, ESGAP (ESCMID Study Group for Antimicrobial stewardshiP). What is antimicrobial stewardship? Clin Microbiol Infect. 2017;23:793-8.
10. Riccardi N, Matucci T, Falcone M. Why don't we talk about tuberculosis stewardship? Clin Microbiol Infect. 2025;31:326-8.
11. Devasia RA, Blackman A, Gebretsadik T, Griffin M, Shintani A, May C, et al. Fluoroquinolone resistance in *Mycobacterium tuberculosis*: the effect of duration and timing of fluoroquinolone exposure. Am J Respir Crit Care Med. 2009;180:365-70.
12. van der Heijden YF, Maruri F, Blackman A, Mitchel E, Bian A, Shintani AK, et al. Fluoroquinolone susceptibility in *Mycobacterium tuberculosis* after pre-diagnosis exposure to older- versus newer-generation fluoroquinolones. Int J Antimicrob Agents. 2013;42:232-7.
13. Chen TC, Lu PL, Lin CY, Lin WR, Chen YH. Fluoroquinolones are associated with delayed treatment and resistance in tuberculosis: a systematic review and meta-analysis. Int J Infect Dis. 2011;15:e211-6.
14. Jacoby GA. Mechanisms of resistance to quinolones. Clin Infect Dis. 2005;41 Suppl 2:S120-6.
15. Olearo F, Both A, Belmar Campos C, Hilgarth H, Klupp EM, Hansen JL, et al. Emergence of linezolid-resistance in vancomycin-resistant *Enterococcus faecium* ST117 associated with increased linezolid-consumption. Int J Med Microbiol. 2021;311:151477.
16. Achermann Y, Eigenmann K, Ledergerber B, Derksen L, Rafeiner P, Clauss M, et al. Factors associated with rifampin resistance in staphylococcal periprosthetic joint infections (PJI): a matched case-control study. Infection. 2013;41:431-7.
17. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic stewardship program: guidelines by the infectious diseases society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62:e51-77.
18. Lee RA, Stripling JT, Spellberg B, Centor RM. Short-course antibiotics for common infections: what do we know and where do we go from here? Clin Microbiol Infect. 2023;29:150-9.
19. Spellberg B, Rice LB. The shorter is better movement: past, present, future. Clin Microbiol Infect. 2023;29:141-2.
20. Thom KA, Tamma PD, Harris AD, Dzintars K, Morgan DJ, Li S, et al. Impact of a prescriber-driven antibiotic time-out on antibiotic use in hospitalized patients. Clin Infect Dis. 2019;68:1581-4.
21. Carratalà J, Garcia-Vidal C, Ortega L, Fernández-Sabé N, Clemente M, Albero G, et al. Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in community-acquired pneumonia: a randomized controlled trial. Arch Intern Med. 2012;172:922-8.
22. Pakyz AL. The utility of hospital antibiograms as tools for guiding empiric therapy and tracking resistance. Insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy. 2007;27:1306-12.
23. Hostler CJ, Moehring RW, Ashley ES, Johnson M, Davis A, Lewis SS, et al. Feasibility and value of developing a regional antibiogram for community hospitals. Infect Control Hosp Epidemiol. 2018;39:718-22.
24. Wald-Dickler N, Holtom PD, Phillips MC, Centor RM, Lee RA, Baden R, et al. Oral is the new IV. Challenging decades of blood and bone infection dogma: a systematic review. Am J Med. 2022;135:369-79.e1.
25. Davar K, Clark D, Centor RM, Dominguez F, Ghanem B, Lee R, et al. Can the future of ID escape the inertial dogma of its past? The exemplars of shorter is better and oral is the new IV. Open Forum Infect Dis. 2023;10:ofac706.
26. Tiberi S, Akkerman O, Sotgiu G, Saderi L, Kunst H, Carvalho AC, et al. Drug management of TB in the intensive care setting: an international multicentre study. Int J Tuberc Lung Dis. 2025;29:340-8.
27. Musisi E, Wamutu S, Ssengooba W, Kasiinga S, Sessolo A, Sanyu I, et al. Accuracy of the tuberculosis molecular bacterial load assay to diagnose and monitor response to anti-tuberculosis therapy: a longitudinal comparative study with standard-of-care smear microscopy, Xpert MTB/RIF Ultra, and culture in Uganda. Lancet Microbe. 2024;5:e345-54.
28. Heyckendorf J, Georghiou SB, Frahm N, Heinrich N, Kontsevaya I, Reimann M, et al. Tuberculosis treatment monitoring and outcome measures: new interest and new strategies. Clin Microbiol Rev. 2022;35:e0022721.
29. Reimann M, Avsar K, DiNardo AR, Goldmann T, Günther G, Hoelscher M, et al. The TB27 transcriptomic model for predicting mycobacterium tuberculosis culture conversion. Pathog Immun. 2024;10:120-39.
30. Sarkar M, Sarkar J. Therapeutic drug monitoring in tuberculosis. Eur J Clin Pharmacol. 2024;80:1659-84.
31. Köhler N, Karaköse H, Grobbel HP, Hillemann D, Andres S, König C, et al. A single-run HPLC-MS multiplex assay for therapeutic drug monitoring of relevant first- and second-line antibiotics in the treatment of drug-resistant tuberculosis. Pharmaceutics. 2023;15:2543.
32. Akkerman OW, Dijkwel RD, Kerstjens HA, van der Werf TS, Srivastava S, Sturkenboom MG, et al. Isoniazid and rifampicin exposure during treatment in drug-susceptible TB. Int J Tuberc Lung Dis. 2023;27:772-7.
33. Brehm TT, Akkerman OW, Sotgiu G, Tiberi S, Chang KC, Dheda K, et al. Clinical standards FOR antimicrobial stewardship in tuberculosis. IJTLD Open. 2025. In press.
34. Weiss K, Blais R, Fortin A, Lantin S, Gaudet M. Impact of a multipronged education strategy on antibiotic prescribing in Quebec, Canada. Clin Infect Dis. 2011;53:433-9.
35. Meeker D, Linder JA, Fox CR, Friedberg MW, Persell SD, Goldstein NJ, et al. Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices: a randomized clinical trial. JAMA. 2016;315:562-70.
36. Baluku JB, Katuramu R, Naloka J, Kizito E, Nabwana M, Bongomin F. Multidisciplinary management of difficult-to-treat drug resistant tuberculosis: a review of cases presented to the national consilium in Uganda. BMC Pulm Med. 2021;21:220.
37. D'Ambrosio L, Bothamley G, Caminero Luna JA, Duarte R, Guglielmetti L, Muñoz Torrico M, et al. Team approach to manage difficult-to-treat TB cases: experiences in Europe and beyond. Pulmonology. 2018;24:132-41.
38. Guglielmetti L, Jaffré J, Bernard C, Brossier F, El Helali N, Chadelat K, et al. Multidisciplinary advisory teams to manage multidrug-resistant tuberculosis: the example of the French Consilium. Int J Tuberc Lung Dis. 2019;23:1050-4.
39. Huang GK, Pawape G, Taune M, Hiasihri S, Ustero P, O'Brien DP, et al. Telemedicine in resource-limited settings to optimize care for multidrug-resistant tuberculosis. Front Public Health. 2019;7:222.
40. Tiberi S, Pontali E, Tadolini M, D'Ambrosio L, Migliori GB. Challenging MDR-TB clinical problems - The case for a new Global TB Consilium supporting the compassionate use of new anti-TB drugs. Int J Infect Dis. 2019;80s:S68-72.

41. Zakhour J, Haddad SF, Kerbage A, Wertheim H, Tattevin P, Voss A, et al. Diagnostic stewardship in infectious diseases: a continuum of antimicrobial stewardship in the fight against antimicrobial resistance. Int J Antimicrob Agents. 2023;62:106816.
42. WHO Consolidated Guidelines on Tuberculosis. Module 3: Diagnosis. Geneva: World Health Organization; 2025.
43. Schwab TC, Perrig L, Göller PC, Guebely De la Hoz FF, Lahousse AP, Minder B, et al. Targeted next-generation sequencing to diagnose drug-resistant tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2024;24:1162-76.
44. Domínguez J, Boeree MJ, Cambau E, Chesov D, Conradie F, Cox V, et al. Clinical implications of molecular drug resistance testing for *Mycobacterium tuberculosis*: a 2023 TBnet/RESIST-TB consensus statement. Lancet Infect Dis. 2023;23:e122-37.
45. Grobbel HP, Merker M, Köhler N, Andres S, Hoffmann H, Heyckendorf J, et al. Design of multidrug-resistant tuberculosis treatment regimens based on DNA sequencing. Clin Infect Dis. 2021;73:1194-202.
46. WHO Operational Handbook on Tuberculosis. Module 1: Prevention - Tuberculosis Preventive Treatment. 2nd ed. Geneva: World Health Organization; 2024.
47. Brehm TT, Köhler N, Grobbel HP, Welling J, Mandalakas AM, Fava V, et al. High risk of drug-resistant tuberculosis in IGRA-negative contacts: should preventive treatment be considered? Infection. 2025;53:1501-6.
48. Polso AK, Lassiter JL, Nagel JL. Impact of hospital guideline for weight-based antimicrobial dosing in morbidly obese adults and comprehensive literature review. J Clin Pharm Ther. 2014;39:584-608.
49. Goletti D, Cirillo DM, Lange C, Tiberi S, Günther G, Petrone L, et al. The empty medicine cabinet: urgent action needed to resolve TB drug shortages in Europe. Int J Infect Dis. 2025;159:108022.
50. Portnoy A, Yamanaka T, Nguhiu P, Nishikiori N, Garcia Baena I, Floyd K, et al. Costs incurred by people receiving tuberculosis treatment in low-income and middle-income countries: a meta-regression analysis. Lancet Glob Health. 2023;11:e1640-7.
51. Neumann M, Reimann M, Chesov D, Popa C, Dragomir A, Popescu O, et al. The molecular bacterial load assay predicts treatment responses in patients with pre-XDR/XDR-tuberculosis more accurately than GeneXpert Ultra MTB/Rif. J Infect. 2024;90:106399.
52. Copaescu AM, Vogrin S, James F, Chua KY, Rose MT, De Luca J, et al. Efficacy of a clinical decision rule to enable direct oral challenge in patients with low-risk penicillin allergy: the PALACE randomized clinical trial. JAMA Intern Med. 2023;183:944-52.
53. Rose MT, Slavin M, Trubiano J. The democratization of de-labeling: a review of direct oral challenge in adults with low-risk penicillin allergy. Expert Rev Anti Infect Ther. 2020;18:1143-53.
54. Buhari GK, Keren M, Dursun AB, Güler M, Dulkar G, Kalaç N, et al. Immediate-type hypersensitivity reactions due to antituberculosis drugs: a successful readministration protocol. Ann Allergy Asthma Immunol. 2015;115:39-44.
55. Sharma RK, Verma GK, Tegta GR, Sood S, Rattan R, Gupta M. Spectrum of cutaneous adverse drug reactions to anti-tubercular drugs and safe therapy after re-challenge - a retrospective study. Indian Dermatol Online J. 2020;11:177-81.
56. Alipanah N, Jarlsberg L, Miller C, Linh NN, Falzon D, Jaramillo E, et al. Adherence interventions and outcomes of tuberculosis treatment: a systematic review and meta-analysis of trials and observational studies. PLoS Med. 2018;15:e1002595.
57. Bermingham WH, Bhogal R, Arudi Nagarajan S, Mutlu L, El-Shabrawy RM, Madhan R, et al. Practical management of suspected hypersensitivity reactions to anti-tuberculosis drugs. Clin Exp Allergy. 2022;52:375-86.
58. Wasserman S, Brust JC, Abdelwahab MT, Little F, Denti P, Wiesner L, et al. Linezolid toxicity in patients with drug-resistant tuberculosis: a prospective cohort study. J Antimicrob Chemother. 2022;77:1146-54.
59. Liu X, Thompson J, Dong H, Sweeney S, Li X, Yuan Y, et al. Digital adherence technologies to improve tuberculosis treatment outcomes in China: a cluster-randomised superiority trial. Lancet Glob Health. 2023;11:e693-703.
60. Gallardo CR, Rigau Comas D, Valderrama Rodríguez A, Roqué i Figuls M, Parker LA, Caylà J, et al. Fixed-dose combinations of drugs versus single-drug formulations for treating pulmonary tuberculosis. Cochrane Database Syst Rev. 2016;2016:CD009913.