



Published in final edited form as:

Lancet Infect Dis. 2026 June ; 26(6): e248–e256. doi:10.1016/S1473-3099(25)00547-X.

Future-Proofing TB Therapy: Framework for Concurrent Drug and Resistance Testing Development

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Summary

The rapid emergence of resistance to novel tuberculosis (TB) drugs, such as bedaquiline, represents a critical threat to the long-term effectiveness of novel regimens. Given that the introduction of these agents has enabled the introduction of an all-oral regimen for rifampicin- and multidrug-resistant TB, the rise of resistance underscores the urgent need to safeguard their efficacy and responsible use. A major barrier is the delay in developing reliable tools to detect resistance to novel compounds, which limits clinical decision-making and surveillance efforts. Herein, we outline a framework for integrating the development of drug susceptibility testing (DST) alongside TB drug development, including early-stage resistance profiling and defining appropriate epidemiological cut-off values. We highlight key gaps, including the need for structured partnerships between drug developers, diagnostic manufacturers, regulators, research institutions, funders, and policymakers. We propose a roadmap to accelerate DST development of new TB regimens, ensuring that resistance detection maintains pace with the introduction of novel drugs. Establishing collaborative platforms for data sharing, genomic analysis, and diagnostic innovation will help ensure that resistance detection evolves in step with drug development, thereby preserving novel treatments and improving global TB care.

Introduction

The World Health Organization's (WHO) 2018 recommendation to move towards all-oral treatment regimens marked a significant shift in the treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB).¹ By 2023, 58 countries adopted the 6-month BPaL(M) regimen—comprising bedaquiline, pretomanid, linezolid, and moxifloxacin—for treating MDR/RR-TB or pre-extensively drug-resistant TB (pre-XDR-TB).² Additionally, 100 countries implemented the 9-month all-oral regimen, which includes bedaquiline and fluoroquinolones, for MDR/RR-TB.²

The development and evaluation of these novel regimens spanned decades, costing the public and private sectors hundreds of millions of dollars.³ Rapid uptake of BPaL(M) was a considerable step towards improving access to therapy and patient outcomes. However, the growing emergence of resistance to bedaquiline remains a high concern.⁴ A recent

retrospective study using whole-genome sequencing (WGS) identified resistance to these drugs in at least 27 countries across four continents.⁵ Similarly, a longitudinal study in South Africa found evidence of acquired resistance to bedaquiline among individuals who had received at least 4 months of a bedaquiline-containing regimen. However, the relative contribution of primary (*de novo*) and transmitted resistance to bedaquiline remains uncertain.⁶ In a national surveillance programme in South Africa, 2.3% of individuals with baseline susceptibility developed resistance to bedaquiline at a median of 90 days.^{7,8} The latest estimates of bedaquiline resistance prevalence among MDR/RR-TB isolates in Mozambique exceed 10%.⁸ In the same programme, bedaquiline resistance halved the odds of a successful outcome. The lack of robust diagnostics to rapidly detect resistance to critical new drugs has been the driving force behind the problem, jeopardising treatment outcomes.⁹

Accompanying diagnostic tests can be characterized as either companion (developed alongside and essential for the administration of new treatments) or complementary. While complementary diagnostics lack a formal regulatory definition, they play a crucial role in supporting antimicrobial stewardship and are widely acknowledged for their importance,^{10,11} including for newly developed TB drugs (Supplementary P1).

Aligning drug development with DST solutions, as recommended by the WHO Target Regimen Profiles, is essential to enable timely detection of resistance and optimised treatment strategies.¹²

Nonetheless, pharmaceutical and diagnostic companies often have misaligned priorities, timelines, and incentives for the final deployment of products. While pharmaceutical companies generally focus on the clinical development and regulatory approval of new drugs, with limited incentive to ensure suitable diagnostic tools are available at launch, diagnostic companies often lack the necessary market incentives or early access to drug resistance data required to develop and validate new tests. This gap delays the availability of scalable DST tools, which are often only considered at a late stage.^{13,14}

Bridging these gaps requires coordination between the pharmaceutical and diagnostic sectors, academia, affected countries, regulatory agencies, and donors. Engagement of the scientific community will be key to generating preliminary data on drug resistance mechanisms during the early stages of drug and DST development. Here, we outline opportunities for earlier alignment between TB drug and DST development, and enhanced collaborations among stakeholders to optimise TB management strategies.

Developing foundational DST profiles for emerging TB therapies during drug development.

A robust laboratory strategy is critical for the development of novel antimicrobial agents. Such a strategy requires an understanding of drug resistance mechanisms, and reliable and standardised DST strategies. This approach requires the systematic generation of data on minimum inhibitory concentration (MIC) distributions across bacterial lineages, using a standardized protocol, alongside work to determine the rate and kinetics of resistance selection. Since each new drug will eventually be incorporated into a treatment regimen, this initial phase will be followed by genotypic studies on the development of drug resistance and analyses of potential interactions with other anti-TB compounds, using *in silico*

modelling and sequencing to build and preserve optimal regimen potency. This process will lead to the development of genotypic DST, external quality assurance (EQA) panels, and systems to facilitate resistance data sharing and standardised analyses (Figure 1).¹⁵

1. Establishing phenotypic drug susceptibility testing strategies: Early engagement between drug manufacturers, laboratory scientists, and regulators is critical for the generation and collation of phenotypic data on novel drugs. Data on stability, solubility, light susceptibility, temperature, humidity, among other physical factors, are essential for investigating diagnostic media compatibility, and determining MIC distributions and epidemiological cut-off values (ECOFFs) - the highest MIC value distinguishing wild-type bacteria from those with phenotypically detectable resistance mechanisms.

Standardising MIC determination for *Mycobacterium tuberculosis* complex (MTBC) is essential for assessing drug susceptibility, ensuring comparability across studies and clinical settings, and guiding treatment decisions. Historically, MIC testing for MTBC has been inconsistent as methodologies and critical concentrations have varied. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has developed a standardised broth microdilution (BMD) method^{17,18} which enhances the reproducibility of MIC testing and facilitates the calibration of commercial and non-commercial methods through which ECOFFs can be reliably established. However, regulators, as the European Medicines Agency (EMA), must now agree on the standards required to evaluate new drugs.

While information on new drug candidates typically resides within the pharmaceutical industry, well-characterised clinical strains are generally only available through clinical or research laboratories. As EUCAST requires data from five independent and proficient laboratories to determine an ECOFF, an international network of laboratories should be established to support drug development and standardise wild-type strain panels for resistance testing. The panels should be made publicly available and regularly updated to facilitate collaboration with industry partners. The early engagement of laboratory experts can support interdisciplinary and cross-sectoral exchange between the pharmaceutical industry, academia, and national or supra-national laboratory services. Legal and confidentiality agreements would be required, but should not pose an insurmountable barrier.

Standardised data templates must be developed to ensure data is collected in a format ready for submission to regulatory authorities.

MIC determination across different MTBC lineages: When establishing ECOFFs for new drugs, it is crucial to consider that MIC distributions can vary by MTBC lineage. For example, MTBC strains belonging to Indo-oceanic ancient Lineage 1 have a higher MIC mean and distribution for pretomanid and pyrazinamide than for other lineages (Supplementary P2).¹⁹ Lineage 3 strains, prevalent in East Africa, India, and Central Asia, have shown differences from other lineages in their MIC distribution for fluoroquinolones.²⁰ In some cases, the same resistance-conferring mutation has been observed to have different effects on MIC in different lineages, as demonstrated by *rpoB* D435V and rifabutin resistance in Lineages 2 (low-level resistance) versus Lineage 4 (wild-type distribution).²¹

While differences in MIC may not influence treatment outcomes, understanding the geographical and lineage-related patterns of pre-existing resistance or shifts in MIC distribution may help inform dose selection decisions and identify clinical trial locations. Genomic studies of resistance mechanisms will, in turn, provide a clearer understanding of how genetic modifications influence clinical outcomes, including cross-resistance to other drugs in the regimen (e.g., as observed with clofazimine and bedaquiline).^{22,23}

Most fluoroquinolone resistance is due to mutations in the *gyrA* QRDR (Quinolone Resistance-Determining Region) with a few *gyrB* mutations responsible for the remainder. Individual mutations in the *gyrA* or *gyrB* genes may lead to low-level resistance but combined their effect can be additive, resulting in higher MICs.²⁴ Thus genomic investigations in conjunction with MIC determination is crucial for guiding appropriate dosage and regimen selection, and preventing the dismissal of potentially effective drugs.

2. Study of drug resistance mechanisms and interaction with other drugs:

Detailed studies of resistance mechanisms are essential to optimise clinical trial design and to anticipate potential limitations of new regimens. Genetic alterations in drug targets are the most common resistance mechanisms to MTBC drugs, impairing their binding and activity (e.g., for rifampicin (*rpoB*), isoniazid (*inhA*), ethambutol (*embB*), streptomycin, aminoglycosides, linezolid (ribosomal protein *rpsL*), and fluoroquinolones (*gyrA*)). Other mechanisms of resistance include mutations of genes encoding drug-activating enzymes (e.g., isoniazid (*katG*), pyrazinamide (*pncA*), ethionamide (*ethA*), pretomanid and delamanid (*ddn*)). Less common resistance mechanisms include the upregulation of drug efflux pumps (Rv0678), which is of importance for bedaquiline and clofazamine.²⁵

Establishing baseline mutation data at the time of drug introduction is essential for understanding resistance patterns and developing effective diagnostic and surveillance tools. Common protocols for data collection must be developed and standardised globally, with National TB Programs (NTPs) taking the lead in gathering information. In TB, the WHO drives these efforts by defining common recording and reporting protocols and housing the data in the MTBC sequencing and phenotyping knowledgebase of the WHO Global Tuberculosis Programme.²⁶

Understanding drug resistance to support drug development: Understanding resistance mechanisms is crucial to collecting baseline resistance data and harmonising surveillance protocols. As each model system (*in vitro* or *in vivo*) has its strengths and limitations, where possible, a comprehensive approach should be adopted, contingent on the stage of development. The first is during the preclinical development phase. To create a catalogue of resistance mutations, data from *in vitro* studies and/or from animal models are required.^{25,27}

Classically, sub-MIC concentration mutation selection experiments are a method for generating drug-resistant mutants.²³ Although the mutants that emerge from these efforts cannot always be expected to reflect that observed *in vivo*, they should at minimum identify the promoter or coding sequences involved in resistance.²⁸ Identification of such mutants will provide the opportunity to screen large public sequence data repositories for genetic

variations across identified genes. Common mutations could be tested phenotypically, either directly where strains are available, or by allelic exchange where they are not. Cross-resistance to other drugs should be tested. Findings would expand the nascent resistance catalogue for the drug in question.

Findings from selection experiments can be expanded upon by modelling the impact of mutations on protein structure and function. Target or pathway protein structures can be derived through x-ray crystallography, cryo-electron microscopy, or through artificial intelligence (AI) programmes such as AlphaFold.²⁹ Changes in structure and function can be modelled using AI and aided by the availability of training data (e.g., from classical selection experiments). For target proteins, molecular simulation approaches can be used to predict changes in drug binding free energy, assessing the likely impact of mutations on drug binding.²⁹

Genomic databases development to study resistance mechanisms: The second stage, before the design of optimal Phase 2b clinical trials, requires an understanding of the prevalence of pre-existing resistance, its geographical distribution, and the associated bacterial population structure.³⁰ This has been facilitated recently by the expanded use of WGS of MTBC clinical isolates for diagnosis of drug resistance and surveillance of TB and MDR-TB transmission.³¹ The adoption of WGS has been considerable in low TB prevalence settings and is increasing in medium and high TB prevalence settings.^{32,33} As of 2025, over 250,000 MTBC sequences are publicly available from the National Centre for Biotechnology Information (NCBI). Several initiatives are now ongoing to link high-quality variant calls to phenotypic DST data. The WHO TB sequencing portal is the most significant of these initiatives, collecting over 55,000 sequenced isolates associated with phenotypic DST (<https://tbsequencing.who.int/download>). These data can facilitate the study of mutation frequency, resistance development, and the prevalence of cross-resistance, thereby supporting the development of new drugs. Some data can be curated to investigate pre-existing resistance associated with bacterial population structure and mapped to global lineage distributions. However, recent resistance requires careful curation and additional sampling for accurate population estimates.

To understand the true prevalence of pre-existing resistance, population-representative data is needed. Many existing collections are based on convenience sampling and although high-quality datasets such as the WHO TB sequencing portal are reasonably representative, additional efforts are still needed. Expanding and diversifying the available datasets would simultaneously facilitate surveillance and validation of mutations in the nascent catalogue, while also screening for yet unknown resistance mutations where both sequencing and phenotypic testing are performed.²⁵ Data on resistance will contribute to decisions about where to conduct relevant clinical trials and which drugs to combine in a trial regimen.

Despite WHO guidance, the sensitivity of genotypic DST for bedaquiline remains suboptimal, suggesting undiscovered resistance mechanisms. To address this, enhanced drug resistance surveillance programs should be systematically integrated with existing WHO frameworks, prioritising isolate collection from treatment failure cases. WGS should be incorporated into resistance mapping efforts through routine sequencing of surveillance

isolates from bedaquiline-containing regimens and validation of *in vitro* findings through comparative analysis of laboratory-selected mutants and clinical isolates.

Prospective cohort studies and Phase 2 clinical trials for new TB regimens should systematically collect paired isolates from patients receiving bedaquiline-containing regimens with parallel genotypic and phenotypic testing. Standardised protocols for MIC determination, WGS pipelines for resistance detection, and unified data formats will be essential. Integration with existing platforms such as the WHO TB sequencing portal will enable real-time comparison of emerging resistance patterns with global databases, providing evidence to refine molecular diagnostics and inform clinical decision-making.

3. Development of diagnostics in preparation for drug introduction into the market: The next stage begins after Phase 2b trials, when a drug is more likely to be approved, and development of rapid and accurate diagnostic tests for drug resistance becomes more urgent.³⁴ Such tests are crucial for individual patient care and monitoring drug resistance in the population. The availability of appropriate DST and testing strategies prior to the routine use of the drug is critical for patient care. However, the timing of diagnostic development will need to be personalised to the specific agent, its relatedness to existing drugs, and the availability of pre-clinical data. While phenotypic drug resistance can be measured *in vitro* and interpreted against pre-established ECOFFs, clinical breakpoints will not likely be calibrated until a much later stage.³⁵ Genotypic assays may be more feasible at this early stage.

The nature of genotypic tests to be developed for rapid resistance detection will depend on the mechanisms of resistance and the strategy for implementing the new drugs and regimens.³⁶ A drug, for example, may lend itself to a PCR or cartridge-based test if the number of resistance-conferring mutations is relatively few or if the genetic determinants of resistance are concentrated in a ‘hotspot’, as is the case for isoniazid and rifampicin. In some cases, the genetic basis of resistance may be more complex, involving multiple genetic loci. This would require alternative approaches, including the development of multiplex PCR methods or the detection of multiple mutations in parallel assays. Sequencing-based approaches are the most obvious solution, whether WGS or targeted next-generation sequencing (tNGS), limited to selected genomic regions of interest.³⁶

While sequencing-based DSTs are comprehensive and have faster turnaround times, their feasibility and cost-effectiveness in high-burden, limited-resource settings require careful assessment. A recent modelling study from India, South Africa, and Georgia found tNGS to be cost-effective, especially where comprehensive phenotypic tests are not routinely conducted.³⁷ When comparing tNGS to in-country DST, tNGS was found to be cost-effective in South Africa and India, but not in Georgia.³⁷ The optimal choice for genotypic DST may therefore be setting-dependent. New tNGS solutions, based on the enrichment and amplification of the entire bacterial genome from clinical samples, are approaching the market.³⁸ These solutions have the advantage that their chemistry is unlikely to need updating each time a new drug target is identified as they already provide data on most of the genome. Only updates to analytic software would be required.

Genotypic solutions, however, must be implemented with clear caveats that their performance has yet to be validated. Only over time, as resistance mutations emerge, can the accuracy of these molecular platforms be confirmed for clinical care and further refined.

The interpretation of rare or novel mutations associated with bedaquiline resistance provides an interesting example. At the time of bedaquiline's introduction, reliable phenotypic DST and a comprehensive understanding of resistance-associated mutations were not available.³⁹ Even today, current testing methods have yet to be calibrated, making it difficult to accurately assess resistance.⁴⁰ While the WHO catalogue has reduced technical uncertainty and interpretation of genomic resistance-determining regions for first-line drugs, data on new and repurposed drugs remains limited.²⁷ Additionally, several mutations remain classified as uncertain significance, requiring further data to ensure the high-quality interpretation within the diagnostic flow. Genotypic tests must therefore be introduced in tandem with a phenotypic assay, and in the context of a referral system that identifies strains at high risk of resistance, such as those from patients experiencing clinical failure, to support the rapid identification of mutations of interest, ultimately reducing interpretation uncertainty.

Novel approaches to data sharing will become essential as pooled analyses allow the expansion of the drug resistance mutation catalogue. Recognising that resistance prevalence is likely to be low at the early stages of using a new drug, an alternative model would be to develop rapid screening tests that can distinguish wild-type from non-wild-type gene fragments and thereby triage relevant samples for comprehensive investigation. This approach also requires a complete understanding of the resistance mechanisms, assuming no cross-resistance (which was not the case for bedaquiline).

To enable rapid and accurate detection of resistance, the development of genotypic DST must focus on identifying key genetic mutations that cause resistance and their corresponding resistance breakpoints. This involves conducting comprehensive mutation analyses and leveraging these insights to inform the development of molecular diagnostics. Rapid data sharing and analysis are equally critical. Available data sharing platforms include the NCBI's Sequence Read Archive (SRA), the European Nucleotide Archive (ENA), and the WHO mutation catalogue which provides a standardised interpretation of genome sequencing results that TB laboratories and test developers can use.²⁵ Engaging public health institutions and healthcare providers in systematic data collection further strengthens the integrity and utility of these systems for both clinical and surveillance needs. Although the sharing of genomic data across jurisdictions and organisations has significant potential advantages, issues such as ownership, privacy and standardisation of accompanying data must be navigated carefully to facilitate this.⁴¹ A strong legal framework should be discussed among parties, and established according to local regulations and laws applicable to the data.

External quality assurance programs are crucial in ensuring the reliability and accuracy of genotypic DST. Early investment in molecular prototypes and expansion of targeted regions by tNGS, is essential to accelerate their availability. Partnerships between researchers,

diagnostic companies, and funders will be necessary to foster innovation and drive development.

Regulatory engagement is also critical for the rapid development and implementation of DST. Regulators will need to both recommend specific studies and data sharing models to enable novel diagnostics, while also streamlining approval processes for new diagnostic tests aligned with new drug development to ensure that genotypic DST tools are rapidly available and accessible in high-burden settings. Collaborative frameworks and donor incentives aimed at engaging developers, regulators, and global health organisations will be essential to achieving this goal.

By prioritising baseline data collection and advancing rapid genotypic DST development, stakeholders can safeguard the long-term effectiveness of new TB drugs while building the diagnostic capacity needed to tackle TB drug resistance.

Monitoring resistance and emergence of resistance

Monitoring the emergence and prevalence of resistance is crucial once a new drug enters clinical use. Without this, treatment programs fly blind, as occurred following the introduction of bedaquiline in many settings. Unrecognised resistance leads to clinical failure and unchecked primary transmission of resistant strains.^{42,43}

Surveys are usually conducted to estimate the prevalence of rifampicin and isoniazid resistance among individuals with TB.⁴⁴ However, a new paradigm estimating resistance to new drugs with a focus on patients with rifampicin-resistant TB is needed. Establishing surveillance systems linked with clinical treatment programmes introducing new regimens is a pragmatic approach, as demonstrated in the South African example.⁴⁵ Cross-sectional and longitudinal surveillance was implemented among individuals starting a bedaquiline-based regimen, to track the prevalence of resistance year-on-year and the emergence of resistance, guiding policy adaptation. The surveillance also facilitated the rapid introduction and decentralisation of routine DST while serving as a platform for the introduction of new drugs or regimens as an ongoing programme activity. The biobanking and sequencing of surveillance isolates can also serve as a local knowledge base for guiding strategic planning and research, as demonstrated in India.⁴⁶ Ensuring such data is shared with global platforms such as the WHO sequencing portal is essential and could serve as a rapid screening system to identify any pre-existing resistance to new compounds.⁴⁷

Phase 3/4 clinical trials should be designed to record and report acquisition of resistance in a standardised way that would allow for pooling and meta-analysis that might stand a chance of identifying a signal. As bedaquiline's history has taught us, even if such events may be rare, they have significant implications for the long-term use of novel drugs.⁴⁸ To enable the pooling of data across studies, it is necessary to standardise trial procedures and definitions, finally generating robust evidence on the frequency and predictors of acquired resistance. This approach would complement programmatic surveillance efforts and inform both clinical decision-making and public health policy.

The Way forward: Creating partnerships to support the process

Given the need to share information on assets in early development, collaboration among the pharmaceutical and diagnostic industries, regulatory agencies, academia, clinical reference laboratories, and donors is essential.⁴⁹ The goal is to create a dynamic ecosystem that facilitates resource sharing, collaboration, and the rapid dissemination of knowledge. To promote the sharing of sensitive information when appropriate, tailored mechanisms, such as ad-hoc tracks, safeguarded by confidentiality agreements, can be developed. These measures are designed to ensure that proprietary information remains protected while enabling knowledge exchange necessary for the successful implementation of the framework.

1. Industry contribution: During the development of anti-TB drugs, the pharmaceutical industry has the responsibility to evaluate a wide range of properties that will determine whether a candidate drug will progress through the development process.⁵⁰ These properties include efficacy, safety, pharmacokinetics, pharmacodynamics, stability, and manufacturability.⁵¹ In addition, regulatory agencies, such as the US Food and Drug Administration (FDA), have developed non-binding recommendations to implement specific studies when developing antimicrobial agents to generate essential (and desirable) outputs that support the progress of the drug through clinical development and aid in the selection of companion drugs.⁵⁰ Key recommended studies identified based on FDA guidance and expanded according to the designed framework are described in Figure 2.

Generally, these outputs are easily applicable and inexpensive, and can facilitate and accelerate drug development by informing the deliberations of the company's multidisciplinary medical development teams. These teams design regimens intended to maximise efficacy while minimising the development of drug resistance and adverse effects. Considerations include: the propensity of drugs to develop resistance; the need to avoid cross-resistance (e.g., through shared cellular targets); the drugs' penetration into TB lesions; the activity against bacterial subpopulations; and overlapping toxicities.⁵⁰ During Phase 2 trials, resistance patterns in bacilli isolated at baseline should be compared to those in bacilli isolated at later stages from participants with treatment failure and recurrence. All gathered information should be made available and will be key to informing the development of diagnostics.

2. Private-private and Private-public partnerships: Financing DST for new TB drugs is a critical, yet often underfunded, element. While donors from public institutions, private sector investments, and philanthropy are pivotal in driving the development of new TB drugs, there is an urgent need to emphasise the importance of early integration of DST development.⁵²

For drug developers, complementary diagnostics should be viewed as fundamental to protect their asset from unchecked resistance development and ensure long-term commercial viability. However, the focus often remains solely on funding the development of the drug itself due to the complex and resource-intensive nature of drug development, and historically limited incentives for TB drug markets. The primary risk of this approach is that DST development is left as an afterthought, hindering the success of new TB regimens. For

diagnostic developers, the requirement to establish a phenotypic assay before advancing to a molecular assay is a significant hurdle. The paucity of manufacturers of materials required for phenotypic DST further slows the diagnostic pipeline, since manufacturing problems experienced by major suppliers can have global repercussions. Addressing this gap requires funding agencies to prioritise funding private-public partnerships and early integration of assay development into the drug development plans. Pharmaceutical companies often have limited access to clinical strains, and establishing MIC distributions requires the engagement of a wider network of proficient laboratories. The engagement of collaborative efforts between funders, developers, academia, and regulators can foster more equitable and scalable solutions for TB DST. Collaborative consortia like ERA4TB, UNITE4TB, R2D2 TB Network, and FEND-TB demonstrate how shared frameworks can disperse costs and risks of drug and DST co-development among different stakeholders, while reducing the burden on pharmaceutical companies. These initiatives are crucial for generating early clinical and molecular data, which are vital for monitoring resistance and validating assays. Moreover, the additional costs involved in DST co-development are relatively modest when compared to the overall investment required for drug development. Dispersed across consortium partners, these costs are manageable while also safeguarding the long-term efficacy and appropriate use of novel TB drugs.

Preventing TB drug resistance through the prompt development and deployment of fit-for-purpose diagnostic tests is a high-yield investment. Philanthropic organisations and private sector contributors can play a catalytic role by earmarking funds specifically for integrated drug and DST development. A holistic approach to financing ensures that breakthroughs in TB treatment achieve their full potential in saving lives.

Conclusions

The development of monitoring strategies to mitigate the emergence of resistance to new drug candidates calls for a transformative approach, beyond traditional research paradigms. We propose a comprehensive strategy to bridge long-standing gaps between drug development and DST, addressing a fundamental weakness in current TB treatment strategies. By aligning the efforts of pharmaceutical companies, diagnostic developers, researchers, and regulatory bodies, we can create a more responsive and adaptive approach to combat drug-resistant TB. The potential impact of this integrated framework extends far beyond immediate clinical improvements. It offers a model for addressing one of the most pressing global health challenges of our time. Early, collaborative mechanisms for information sharing, genomic analysis, and diagnostic development, can significantly reduce the risks associated with emerging resistance and optimise treatment outcomes for TB patients.

Partnerships are a cornerstone of this approach. The complex landscape of TB drug resistance requires a level of coordination that transcends traditional institutional boundaries. Ideally, pharmaceutical companies, research institutions, NTPs, and global health organisations must create a unified, purpose-driven ecosystem of knowledge sharing and innovation in which everybody stands to benefit. This approach requires information, data, and reagents to be protected by confidentiality and material and data agreements

to facilitate the exchange. The Facilitating Accelerated Science and Translation for TB Regimen Development (FAST-TB) program, through the Knowledge Integration for TB Treatment Development (KITT) Track, has established such a forum.⁵³

Regulatory bodies play a crucial role in this transformation, providing guidelines to facilitate rapid, yet responsible, development of both drugs and diagnostic tools. With an estimated 400,000 MDR/RR-TB cases annually, and less than half diagnosed and treated, the urgency of this challenge cannot be overstated. Our proposed framework offers a structured pathway to address these critical gaps, emphasising not only scientific innovation but a holistic approach that considers epidemiological, clinical, and programmatic realities.

The TB research community at large must adopt a more integrative and collaborative model of research and development, which necessitates not only scientific expertise but also meaningful engagement with civil society, patient communities, and local healthcare providers.

Our framework aims to operationalise this vision by providing a concrete, collaborative model for accelerating the development, validation, and deployment of resistance testing tools aligned with the evolving landscape of TB drug regimens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

“This paper is published within the context of FAST-TB, a program supported with funding from the National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) and National Science Foundation (NSF) through agreement number INT-9531011. The content is solely the responsibility of the authors and does not necessarily represent the official view of the NIH and/or CRDF Global.”

Declarations of interest

AY is employed by GSK and hold financial equities in GSK. BK received funding from CRDF Global for time devoted to having meetings and compiling the manuscript; received royalties from SmartSpot Quality for provision of diagnostic verification controls for drug resistance TB diagnostics.. CMD received NIH funding via UCSF (Grant number: U01AI152087); Grants: FIND, Geneva: Various projects on TB diagnostics development and evaluation; German Center for Infectious Disease Research (DZIF): Various projects on TB diagnostics development and evaluation; Member of the WHO Advisory Group in Tuberculosis Diagnostics and Laboratory Strengthening, Vice Chair in Heidelberg & TB Co-Chair of DZIF. SY has been, through the NIAID grant U01AI152087, involved in clinical studies of multiple tuberculosis diagnostics, Scientific Editor of PLOS Medicine Magazine.

All other authors have no conflict of interest

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Key Points

Drug Resistance is outpacing detection tools:

New TB drugs face rapidly emerging resistance, but diagnostic tools to detect it are often developed too late.

Drug and diagnostics companies' misalignment:

Pharmaceutical and diagnostic companies have different priorities and timelines, leading to delayed availability of DST at drug launch.

Critical need for co-development:

Drug development must be paired with early DST profiling (both phenotypic and genotypic) to detect early emergence of resistance and to ensure optimal use of the new compounds and regimens

Proposed framework:

Early partnerships and collaborative platforms for data, reagents, and genomic analysis can align drug and DST pipelines, safeguarding treatment success.

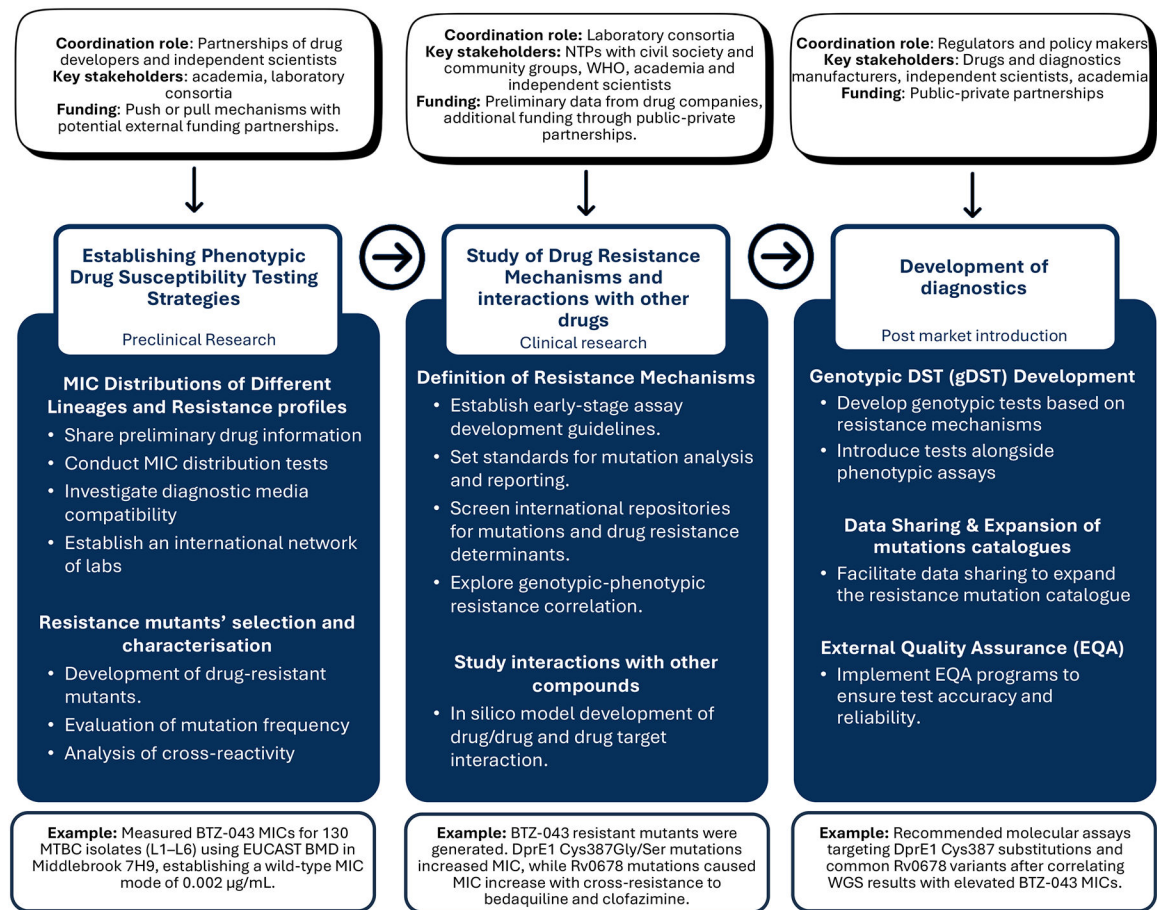


Figure 1: Framework for the development of DST for new compounds from the early stages of drug development to post-market introduction.

Three key phases include: (1) establishing phenotypic DST strategies, including MIC distribution studies and mutant selection and characterisation, (2) studying genomic drug resistance mechanisms and interactions with other drugs, and (3) developing diagnostics post-introduction of the drug to the market. Examples are cited from¹⁶

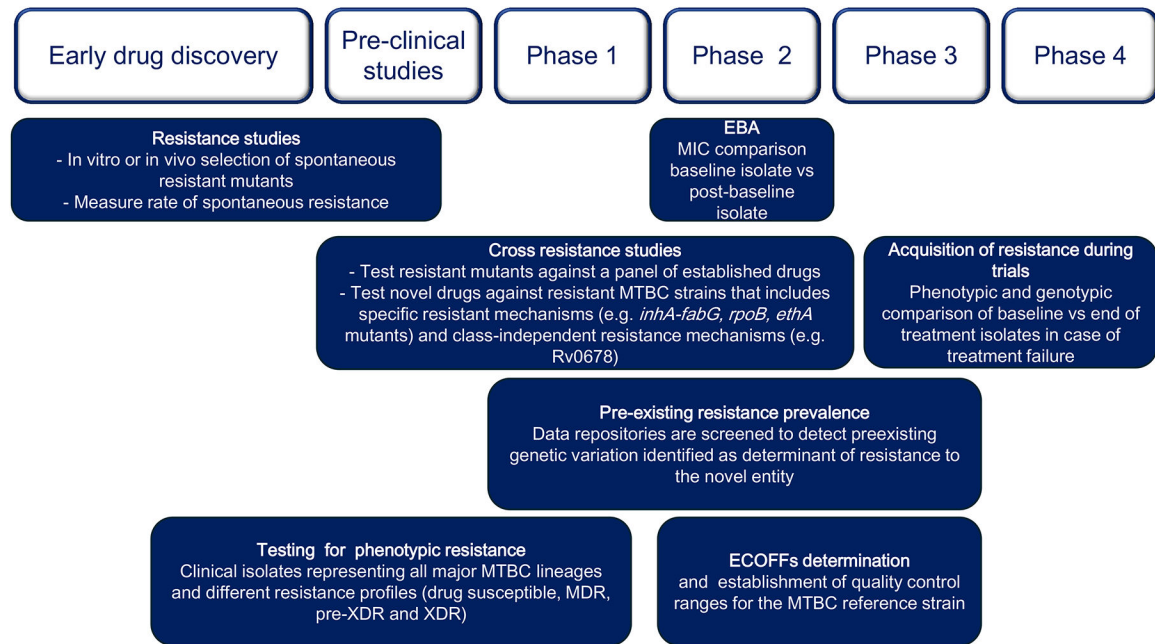


Figure 2: Integration of resistance-related studies across the drug development pipeline for tuberculosis.

White boxes indicate the phases of drug development, while blue boxes feature the recommended studies for pharmaceutical companies to investigate the development of resistance to new compounds. Studies spanning from early drug discovery to Phase 3–4 trials include spontaneous resistance selection, cross-resistance profiling, testing against diverse clinical isolates and lineages, and determining epidemiological cut-off values (ECOFFs). Acronyms: ECOFFs: epidemiological cut-offs; EBA: early bactericidal activity; MDR: multi-drug resistant; MTBC: Mycobacterium tuberculosis; pre-XDR: pre-extensively drug resistant; XDR: extensively drug resistant (according to WHO 2021 definitions⁹)