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Editorial

Beyond the Culture Plate: Accelerating Genomic Revolution in Global Mycobacterial Surveillance

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Abstract

To achieve global tuberculosis elimination, the international framework must prioritise proactive genomic and digital surveillance. Current traditional diagnostics facilitate underreporting of drug-resistant strains of *M. tuberculosis* in high-burden regions, promoting the cross-border transmission of XDR-TB. This editorial outlines an actionable, next-generation surveillance strategy to mitigate the diagnostic gaps and curtail the global spread of drug-resistant pathogens.

***Keywords**: Tuberculosis; Multi-Drug Resistance; Genomics; Public Health Surveillance; Disease Elimination; XDR-TB*

Tuberculosis is one of the top ten causes of death from a single infectious pathogen worldwide, accounting for 1.23 million deaths globally [1]. Notably, the post-pandemic years show a slight 3% decline in mortality, suggesting that the world is still in convalescence from COVID-19 disruption [2]. The World Health Organisation (WHO) reported that global TB incidences stand for 10.7 million in the 2026 tracking year. TB is unevenly distributed, with 30 high-burden countries accounting for 87% of new tuberculosis infections, including South East Asia (38%), the Western Pacific (26%) and Africa (23%) [3]. These metrics indicate that modern public health systems can measure standard tuberculosis infection, but they struggle to map the highly lethal transmission chain of resistant strains. Key findings showed that 8.3 million cases were diagnosed globally, with a surveillance gap of 2.4 million missing or unreported cases [4]. The numbers support recent effective advances in diagnostics and the scale-up of rapid molecular testing such as Xpert MTB/RIF over lengthy phenotypic culture methods.

However, the true challenges remain with drug-resistant TB. Strikingly, the WHO 2026 surveillance cycle reported 390 000 cases that combined MDR-TB/RR-TB, with only 42% of patients having access to proper treatment [5]. In this context, true multidrug-resistant tuberculosis comprises resistance to both rifampicin and isoniazid, accounting for 78% of cases, with the remainder comprising rifampicin (RR-TB) monoresistance [6,7]. The epidemiological data reveal a dual threat, with 19% of cases showing acquired resistance among those with a history of prior anti-TB therapy; however, 4.1% of patients have primary transmission of MDR-TB/RR-TB, accounting for naive drug-resistant strains [8]. At the host-pathogen interface, the incidence of acquired resistance emphasises a systemic failure in clinical management and public health delivery. Evolutionary phylogenetic analyses of *M. tuberculosis* show rare horizontal gene transfer and chromosomal mutations selected from spontaneous variation under drug pressure [9]. A health system characterised by an erratic drug supply, substandard pharmacology and fragmented patient adherence creates opportunities for transmission, resulting in the development

of sub-therapeutic windows that serve as an evolutionary filter [10]. These phenomena promote the eradication of drug-susceptible bacilli in favour of naturally occurring resistant sub-populations of bacilli, such as *rpoB* resistance to rifampicin and *KatG/inhA* resistance to isoniazid, and enable the unrestricted replication of *M. tuberculosis* strains [11]. These data indicate that drug resistance is not only a matter of poor patient compliance associated with treatment failure, but rather an independent transmission and worldwide cause of sub-epidemic [12].

Dependence on fragmented diagnostic pipelines and slow phenotypic drug susceptibility testing (DST) is driving the rise in multidrug-resistant strains to pre-XDR and XDR-TB [13]. Notably, DST requires four to six weeks to deliver a complete antimicrobial profile, creating a clinical gap. Consequently, these hidden resistant strains of MDR are treated with a standard first-line or empirical short-course regimen during this period [14]. This unbalanced treatment serves as an evolutionary selective advantage for the natural mutant, which permits the elimination of the drug-susceptible population that is in contact with the naturally occurring mutant population in the presence of sub-lethal drug concentrations, thereby maximising selection of drug resistance phenotypes in TB strains for survival [15-17].

The primary disadvantage of standard GeneXpert assays (such as Xpert MTB/RIF and Xpert/Ultra) is their inability to detect resistance to second-line tuberculosis drugs, as the cartridge is strictly limited to detecting rifampicin resistance [14]. XDR-TB involves resistance to rifampicin, isoniazid, and fluoroquinolones, as well as one of the modern core drugs, such as bedaquiline and linezolid, which requires a special Xpert MTB/XDR cartridge [14]. This Xpert MTB/XDR detection has a significant molecular blind spot due to its inability to detect all foundational drugs implemented in modern XDR-TB regimens, such as oral bedaquiline, linezolid and pretomanid (e.g. BPaL). Furthermore, it exhibits lower sensitivity (less than 75%) to amikacin and second-line injectable drugs compared with standard phenotypic testing [16,18]. This also completely overlooks rare, non-canonical genetic mutations outside of its target probe zone. The Xpert MTB/XDR can also result in false-positive resistance in patients with prior clinical history, with a sensitivity and specificity of 93% and 98%, respectively, as compared to DST, due to the presence of dead bacilli [17]. Furthermore, another disadvantage of Xpert MTB/XDR is its reduced analytical sensitivity in the case of paucibacillary specimens with low bacterial loads. This technical limitation supports the view that traditional culture-based drug susceptibility testing (DST) or whole-genome sequencing remains necessary to fully confirm an XDR-TB profile [19].

Whole-genome and next-generation sequencing have been implemented to revolutionise tuberculosis management, delivering a dual advantage that substantially addresses the limitations of traditional molecular assays. By providing a comprehensive drug resistance profile across a broader panel of medicines while simultaneously enabling high-resolution transmission tracking, these technologies offer unprecedented precision for individual treatment and surveillance [20]. Firstly, they can scan vast genomic regions to predict complex resistance to novel XDR-TB drugs such as bedaquiline, linezolid and pretomanid. Consequently, by tracking genetic disparity, sequencing serves as a molecular GPS that maps a concise pathogen transmission chain in near real time, pinpointing outbreaks, differentiating reactivation from reinfection, and actively preventing community spread [21]. However, for resource-limited countries, an optimal solution for managing XDR-TB is a centralised hub-and-spoke laboratory model that leverages post-COVID infrastructure for targeted Next-Generation Sequencing (tNGS). In this approach, XDR-TB is detected using a point-of-care cartridge (Xpert MTB/XDR or Truenat) to detect standard fluoroquinolone and first-line resistance. Samples requiring any complex resistance profiling are then sent to a centralised laboratory equipped with tNGS. This allows low- and middle-income countries to accurately detect resistance to modern drugs such as bedaquiline and map local transmission chains at the low cost of whole-genome sequencing, while preserving extensive sequencing resources for targeted epidemiological surveillance [22].

The call to action

The international motivation to eradicate tuberculosis is constrained by a profound diagnostic paradox. Global policymakers have shown unprecedented political will; however, implementation is bottlenecked.

The basic flaws in this strategy are not due to a lack of therapeutic availability but rather a serious lack of real-time surveillance. The international community can eliminate a pathogen that is inaccurately mapped in real time. The primary obstacle to surveillance of drug-resistant tuberculosis is its heavy dependency on legacy diagnostic pipelines. Notably, in high-burden tuberculosis regions, an overwhelming number of drug-resistant tuberculosis cases are underreported or undetected. In this context, a health system depends on a delayed phenotypic drug resistance test (DST) or a molecular assay to screen for single-drug resistance (e.g. rifampicin), resulting in patients being treated with an inadequate regimen. This approach by the healthcare system not only harms patients' outcomes but also promotes the circulation of pre-XDR and XDR strains in the community. Further, the lack of digital cross-border case-based surveillance internationally promotes the global migration of drug-resistant tuberculosis.

To meet the global TB elimination benchmark, the strategy must span from active diagnosis to proactive genomic surveillance. To execute this strategy, three approaches are essential: first, high-burden countries must prepare to sequence samples directly. Second, a cloud-based digital surveillance platform is needed to ensure no drug resistance is missed. Third, global healthcare authorities must allocate resources equally among all nations, treating baseline diagnostics as a necessity for healthcare systems.

Therefore, the global surveillance system must be proactive to map resistance mutations faster than *M. tuberculosis* can evolve; eradication targets will be moving goalposts. The strategy urges international public health systems to stop the epidemic from hurtling forward and to sequence the bacilli.

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