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Role of Sequencing in Multidrug-Resistant Tuberculosis Surveillance: Bangladesh Perspective

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Multidrug-resistant tuberculosis (MDR-TB) continues to be a significant public health issue worldwide, especially in high-burden countries like Bangladesh. Despite significant progress in TB control, the rise of MDR-TB, which is resistant to at least isoniazid and rifampicin, poses a serious threat to these advancements. Effective surveillance is crucial for controlling the spread of MDR-TB, and genomic sequencing has emerged as a groundbreaking tool in this fight. By offering detailed insights into drug resistance and transmission patterns, genomic sequencing has the potential to transform the surveillance and management of MDR-TB in Bangladesh.

Bangladesh ranks among the top 30 high TB burden countries globally, with an estimated 360,000 new TB cases annually[1]. The Shorter Treatment Regimen for MDR-TB, known as the "Bangladesh Regimen," was introduced by Bangladesh and received global recommendations, including WHO endorsement, in April 2017. While the country has made strides in TB detection and treatment, MDR-TB poses unique challenges. In 2019, it was estimated that there were 3,300 cases of MDR, but only 1,400 (42.4%) patients received a diagnosis, and of those, 1,200 (85.7%) initiated second-line treatment[2-3]. The current detection rate of MDR-TB cases is as low as 34.0% cases[4]. In the second Drug Resistance Survey (DRS) conducted in 2018 to 2019, the prevalence rates of Rifampicin resistance were found to be 0.7% among new cases and 11.4% among previously treated cases[2]. Among the patients with Rifampicin-resistant (RR) tuberculosis, 82.1% cases also showed resistance to Isoniazid, while 21.4% cases had any form of fluoroquinolone (FQ) resistance[4]. The treatment success rate for these patients was 67.0% cases, with a death rate of 17.2% cases, 4.3% cases lost to follow-up, and a failure rate of 4.3% cases[5].

Conventional phenotypic DST was the gold standard for DR-TB diagnoses, but it is time-consuming and labor-intensive. Rapid molecular tests, such as the GeneXpert and line probe assays, have been adopted as diagnostic alternatives for *Mycobacterium tuberculosis* detection and DR prediction[6]. Nevertheless, these assays could only detect a limited number of mutations and show low sensitivity for hetero-resistant strains with variant frequencies below 5.0% to 50.0% cases[7].

This gap underscores the necessity for more advanced tools like whole-genome sequencing (WGS), which provides comprehensive data on Mycobacterium tuberculosis (M. tuberculosis) resistance mechanisms. WGS enables the identification of single-nucleotide polymorphisms (SNPs) and insertions and deletions (indels) in loci associated with drug resistance and is proven to have higher accuracy than phenotypic DST[8]. Sequencing offers significant advantages in monitoring MDR-TB. WGS provides comprehensive resistance profiling by identifying mutations related to both first- and second-line drugs. Unlike line probe assays (LPAs) or GeneXpert®, WGS can detect mutations in less commonly targeted regions, including resistance to all the current first-line, second-line, new and repurposed drugs like bedaquiline (BDQ), linezolid (LZD), delamanid (DLM), and clofazimine (CFZ). With WGS, National Tuberculosis Control Program (NTP) of Bangladesh could gain an unprecedented ability to identify drug-resistant strains and adapt treatment regimens accordingly. This capability is especially important in Bangladesh, where standardized treatment regimens

can result in mismatched therapies and poor patient outcomes.

It will help us understand transmission dynamics and provide accurate, comprehensive data on drug resistance for MDR-TB. This information can inform personalized drug therapy to optimize treatment outcomes[6]. Bangladesh's high population density facilitates the rapid spread of TB, including MDR-TB. WGS enables strain typing, allowing for the identification of transmission clusters and the targeting of high-risk populations or geographic hotspots. This information is invaluable for targeted interventions, including active case finding and infection control measures in healthcare and community settings[4]. Sequencing acts as an early warning system for detecting new patterns of resistance. By continually analyzing genomic data, public health authorities can identify resistance mutations before they become noticeable. This allows for timely adjustments to treatment protocols, helping to prevent the spread of drug resistance[1].

Implementing sequencing-based surveillance in Bangladesh presents several challenges despite its potential benefits. One major barrier is the high cost involved; sequencing requires substantial initial investments in equipment, reagents, and infrastructure. Additionally, there is a shortage of trained personnel skilled in sequencing, bioinformatics, and data interpretation. Moreover, large-scale sequencing generates vast amounts of data, which necessitates the establishment of robust computational infrastructure and effective data-sharing frameworks.

There are several strategies that Bangladesh can adopt to overcome these challenges. Strategic investments and collaborations are key to addressing these issues. Partnerships with global initiatives, such as the Global Fund and the WHO's "End TB Strategy," can offer both technical and financial support. Public-private partnerships can help reduce costs and improve access to sequencing technology. Furthermore, fostering regional collaborations with neighboring countries that face similar challenges can also be beneficial through sharing knowledge and building joint capacity.

Integrating sequencing technology into MDR-TB surveillance offers a significant opportunity to improve TB control in Bangladesh. It allows for effective resistance profiling, tracking transmission, and monitoring emerging resistance, aligning with the goal of TB elimination. Despite some challenges, the benefits of this technology far outweigh the costs. With strategic investments and international collaboration, Bangladesh can strengthen its fight against MDR-TB, protecting public health and moving closer to a TB-free future.

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