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Best approaches to drug-resistance surveillance at the country level

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ABSTRACT

In 2014, the World Health Organization (WHO) recommendation to include the endorsed rapid molecular technologies (Xpert MTB/RIF, line probe assays) into surveillance systems and surveys allowed the testing of more tuberculosis (TB) patients for drug resistance at country level than ever before. The whole genome sequencing (WGS) approach is emerging as a more powerful tool for epidemiological and drug-resistant routine surveillances, promising a rapid and simultaneous screening of all the clinically-relevant mutations for the determination of resistance to the first-, second-line, and new anti-TB drugs. In addition, WGS can support the conventional contact tracing for epidemiological studies with high discriminatory power by tracking the circulating strains and their relatedness. These features make WGS, moreso than the conventional molecular tools, an ideal tool to monitor transmission and drug resistance trends in countries, providing deep and wide information in a standardized way.

WGS technologies have already been adopted in many supranational and reference laboratories at the centralized level, and several research groups are working to reduce the complexity and costs of these platforms, from sample preparation to the downstream analysis and interpretation of sequencing reads, with the final aim to expand the use of WGS to all laboratory levels. The landscape of the platforms available for next-generation sequencing (NGS) is rapidly enriching. It includes high-throughput instruments that can be used for centralized surveillance studies on a large scale, and "benchtop" sequencers that conversely can reach more peripheral settings for rapid and non-extensive surveys.

Traditionally, WGS is performed on genomic DNA samples extracted from clinical isolates to ensure the required high DNA quality and quantity for the following library preparation and sequencing reaction steps. Nevertheless, the researchers are trying to apply the WGS to early primary cultures and in particular directly to sputum samples, including specific procedures to remove non-mycobacterial genetic material and to enrich the *Mycobacterium tuberculosis* (MTB) genome. The targeted NGS approach that takes advantage of the amplification of selected regions of the MTB genome for genotyping and drug resistance determination could represent the most effective method to avoid the need of culturing MTB prior to sequencing, also enabling the implementation of NGS for surveillance purposes in resource-limited settings without infrastructures and equipment for growing TB cultures.

Classical sequencing and NGS approaches have been successfully used in a recent study conducted in five countries with high burden of TB and multidrug resistant tuberculosis

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(MDR-TB) and aimed at investigating levels of resistance to pyrazinamide among patients with TB by *pncA* sequencing [doi: 10.1016/S1473-3099(16)30190-6]. This work innovatively demonstrated that the establishment of strong links between national (peripheral and reference laboratories) and supranational laboratories, with the former possibly processing indirect or direct samples and generating sequencing data, and the latter supporting them for bioinformatics analysis and data interpretation, will soon make WGS and targeted NGS the preferred tools to conduct public health surveillances in TB field, thus helping the strategies adopted by TB control programs at local and national levels.

Conflict of interest

The authors have no conflicts of interest to declare.

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