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Abstract (oral session)

Whole-genome sequencing for rapid identification, antimicrobial susceptibility testing, and typing of extensively drug-resistant Mycobacterium tuberculosis

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Objectives: An estimated 650,000 cases of multidrug-resistant tuberculosis (MDR TB) occurred worldwide in 2010, of which 9% were extensively drug-resistant (XDR). Efforts to contain drug-resistant TB depend on the rapid detection and effective treatment of cases, together with public health interventions to prevent and investigate ongoing transmission. The necessary laboratory support for these activities includes the identification of Mycobacterium tuberculosis complex (MTBC), antimicrobial susceptibility testing, and bacterial genotyping. However, it typically takes between one to two months to achieve all of these goals using traditional techniques. Whole-genome sequencing (WGS) has not been a viable option to accelerate this process because MTBC had to be grown for several weeks before sufficient DNA could be obtained for sequencing. Methods: We have developed a method that allows WGS directly from positive Mycobacteria Growth Indicator Tubes (MGITs), which are routinely used to isolate MTBC. We used this technique to investigate a case of XDR TB using a rapid bench-top sequencing platform, which we compared to standard techniques. Results: The WGS data allowed us to identify the precise genotype of MTBC and provided an accurate prediction of phenotypic resistance. It also demonstrated that the patient was infected with two independent strains of XDR TB (at a ratio of 7:3), which was not apparent based on Multilocus Variable Number Tandem Repeat Genotyping (MIRU-VNTR), the current standard for typing MTBC in the United Kingdom (UK). Moreover, we modelled a mutation that was only found in the alanine racemase of the minority strain. This suggested that the minority strain might be resistant to cycloserine, which was used to treat the patient in question, despite the fact that no phenotypic susceptibility testing for this drug is offered by the reference laboratory in the UK. Conclusion: Rapid WGS directly from positive MGIT tubes represents a paradigm shift for TB diagnostics by allowing the simultaneous identification, drug susceptibility testing, and typing of MTBC. Although the cost-effectiveness of this approach remains to be determined, we believe that this method will become the standard of care in well-resourced countries.