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Letter to Editor

Trace Result in Xpert MTB/RIF Ultra: A Diagnostic Dilemma and Interpretation?

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With the development and implementation of newer diagnostic modalities for diagnosis of tuberculosis, issues related to interpretation and implication of these results in clinical context have created a new hurdle in front of clinicians and program managers. Apart from the presently approved ones, there are many diagnostic tools awaiting approval from WHO for their use in high burden, resource-limited countries [1].

In year 2010, WHO approved a semi-automated nucleic acid amplification test (NAAT) labelled as Xpert MTB/RIF (Xpert) or GeneXpert (Cepheid, Sunnyvale, CA, USA) which detected the presence of Mycobacterium tuberculosis (MTB) complex along with resistance to rifampicin (RIF), based on rpo B gene beacon based hemi-nested PCR method. During early phases of Xpert roll out an error (code 5011- Signal Loss Detection Error) was reported in >5% cases along with few instances of unreliable resistance results. To overcome these issues, G4 version of Xpert cartridge was introduced with updated software and modified probe/wild type target hybrid. This was approved and rolled out in December 2011 by WHO [2]. But needless to say Xpert still had few shortcomings specially in scenarios where bacillary load was not that high. Therefore, to further improve the diagnostic efficiency and utility of their earlier assay, Cepheid came up with the latest version of Xpert i.e. Xpert Ultra cartridge which could be used in the pre-existing GeneXpert® platform [3]. The new cartridge had two significant changes; first was with respect to improvement in DNA amplification process, for this the chamber volume was increased from 25 µl to 50 µl and second was introduction of IS1081 and IS6110 insertion sequences. Thus, it was stated that with these two changes, the MTB detection limit increased drastically from 131 bacilli/ml of sputum to 16 bacilli/ml. Additionally, the overall turnaround time had also been decreased by 77 minutes for the amplification of MTB genetic materials. In Xpert Ultra, semi-quantitative results are categorized as high, medium, low and very low, along with introduction of a new term labelled as "Trace" and RIF resistance status is classified as detected, not detected, or intermediate [4].

With progressive improvement in assay quality, Xpert Ultra has improved detection rates with similar sensitivity patterns, all within a shorter turnaround time thus enabling quicker initiation of anti-tubercular therapy and breaking the chain of transmission. According to the manufacturers, 'Trace' result in Ultra occurs due to low bacillary load in test specimen. The 'Trace' result implies that only the genes IS6110 and IS1810 were detected and amplified but the more pivotal rpo B gene could not be detected. This new semi-quantitative category in Xpert Ultra i.e. MTB Trace, increased its sensitivity by 5% but decreased the specificity by 3.2% as compared to Xpert [4]. As per WHO recommendations, Ultra gives results in all types of smear-positive and negative respiratory specimens similar to previous version of Xpert kit. In a recent study by Mishra., et al. it was reported that Trace results were seen mostly in previously treated tuberculosis patients, whose culture results were mostly negative thereby leading to suboptimal specificity. However, the specificity was improved by 5-15% if all such results was re-categorized as MTB not detected [5].

From patient care and public health point of view, 'MTB-Trace' result in Xpert Ultra limits its utility, particularly in a high tuberculosis prevalent region owing to its low specificity. Similarly, in a scenario where getting a sample itself is a matter of concern like in most extra-pulmonary tuberculosis cases, the presence of a "Trace" result may open up a Pandora's box. As previous studies have clearly shown that most Trace positive patients had history of treatment for tuberculosis in recent past, any such result in a high disease burden country like India warrants interpreting it in terms of the degree of pretest clinical suspicion, presence of epidemiological risk factors, duration since last anti-tubercular therapy intake along with a vigilant follow up of culture results so as to avoid over zealous treatment initiation and therapy related complications. Detailed studies encompassing all relevant factors as mentioned above will shed light on exact utility of this new diagnostic modality, available on an older but widely accessible platform.

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Conflicting Interest

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