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Editorial

Totally Drug Resistant Tuberculosis (TDR-TB): Has its Existence been Conclusively Proved?

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While much has been written on the discovery of Totally Drug-Resistant Tuberculosis (TDR-TB) patients, only a few cases have actually met the stringent criteria which could qualify a patient as a case of TDR-TB. One such study from Italy [1], came very close to reporting 2 cases of TDR-TB. In this study, one patient was tested for all the primary and nearly all the second-line drugs (18 drugs in all) with the exclusion of dapsone, clarithromycin and thiacetazone, while the second patient was tested for all the known anti-TB drugs including dapsone, clarithromycin and thiacetazone.

While other such cases may certainly exist in different parts of the world, most studies have as yet failed to conclusively prove the presence of TDR-TB and have actually reported XDR-TB as TDR-TB which is factually incorrect. In 2012, a study from India too claimed to have discovered 4 cases of TDR-TB. However, on close review of these patients it was evident that only 12 drugs from the primary and second-line tuberculous regimes were tested for drug sensitivity, which certainly did not qualify these patients as cases of totally drug-resistant tuberculosis (TDR-TB), but rather XDR-TB.

The term 'totally drug-resistant' (TDR) has not yet been clearly defined for tuberculosis. While the concept of 'total drug resistance' can be easily understood, in reality, *in-vitro* drug susceptibility testing (DST) is technically difficult and limitations exist. However, DST for the drugs that define MDR and XDR-TB has been studied in detail and a consensus has been reached on the correct methods to be used, critical drug concentrations that define resistance, and reliability and reproducibility of testing [2].

Unfortunately, data on the reproducibility and reliability of DST for the remaining second-line drugs (SLDs) are much more limited and have not been clearly established and the methodology for testing for some does not exist. Moreover, correlation of *in-vitro* DST results with the clinical response to treatment has not yet been conclusively proved either. Therefore, *in-vitro* resistance of a strain of TB bacilli to DST would not necessarily mean that the patient would not be susceptible to these drugs *in-vivo*, and would necessarily not show an adequate clinical response to treatment with this medication. Consequently, the clinical relevance of *in-vitro* drug resistance without internationally accepted and standardized drug susceptibility testing remains unclear and current WHO recommendations therefore advise against the use of these results as the sole guide to treatment [3].

Moreover, newer drugs such as bedaquiline and delamanid have now been discovered for the treatment of MDR-TB and XDR-TB and their effectiveness against suspected 'totally drug- resistant' strains though encouraging, has as yet to be conclusively determined.

As a result, the phrase 'totally drug-resistant tuberculosis' (TDR-TB) has not yet been officially established or recognised by the WHO.

Conclusion

While admittedly MDR-TB and XDR-TB are of immense public health importance, and this cannot be emphasized enough, it is only fair that these cases not be frivolously termed TDR-TB without adequate and indisputable proof that such patients are actually resistant (both *in-vitro* and *in-vivo*) to all known anti-TB drugs which include all primary, second-line as well as other additional drugs known to have good anti-TB action such as rifabutin, clofazimine, dapsone, clarithromycin, thiacetazone and augmentin.

It should be emphasized that the mere presence of drug resistance to 'all available tested drugs' at an institution does not justify or automatically confer the status of TDR-TB in a particular patient.

Lastly, it must be remembered that the mention of the presence of TDR-TB creates a certain sense of anxiety and panic in the general public. Hence we must be careful not to rush to label a patient as a case of TDR-TB until mechanisms are in place to unequivocally detect such cases with the highest degree of accuracy. At present, even the best facilities available help us to accurately detect MDR-TB, XDR-TB and XXDR-TB with a fair degree of accuracy, but not TDR-TB, as stringent criteria (as mentioned above) need to be fulfilled before making a definitive diagnosis of TDR-TB.

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