**Defining pretomanid critical concentration (CC) for phenotypic drug-susceptibility testing (DST) methods**

WHO headquarters, Geneva, Switzerland
1-2 December 2022

## Concept note

Phenotypic methods to detect resistance to anti-TB drugs are based on assessment of ability of the *Mycobacterium tuberculosis* to grow in culture media containing critical concentrations (CC) of specific anti-TB agents (which indicates resistance) or, conversely, its inability to grow in the same media (which indicates sensitivity). Sensitivity is used as a proxy for successful treatment outcome, whereas resistance, a proxy for treatment failure.

# Minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial agent that prevents growth of a microorganism in a solid medium or broth dilution susceptibility test. The Epidemiological cut-off value (ECOFF) is the MIC that corresponds to the upper end of the pWT distribution (i.e. it typically encompasses 99% of pWT strains) and used to define WHO CC. Ideally for break point setting other information should be considered including pharmacokinetic and pharmacodynamic data as well as clinical outcomes. The association between a drug MIC and outcome for TB is not straightforward, however, as multi-drug regimens are used.

A new anti-TB agent (pretomanid) is being put into use for the treatment of M/XDR-TB. DST method is needed to monitor for the emergence of resistance to this anti-TB agent, as it has the potential to improve successful treatment outcomes for patients and reduce the duration of treatment.

## Objective

* To review evidence (published and unpublished) on minimal inhibitory concentrations (MICs) to determine the ECOFF(s), assess the association of the ECOFF(s) with clinical outcome data (where available) and lineage in order to define pretomanid CC for MGIT, 7H10, 7H11, LJ methods.