Updated WHO definitions for tuberculosis outcomes: Simplified, unified and future-proofed

Standardised outcome definitions are crucial for monitoring and comparing effectiveness of treatment strategies for tuberculosis (TB) over time and across geographies. The World Health Organization (WHO) has played a leading role in developing such definitions for programmatic evaluation and has published the *Definitions and reporting framework for tuberculosis* as a document to guide harmonisation of data collection and reporting practices.[1] Periodic revision of such definitions are necessary to keep up with scientific progress and changes in clinical practice,[2,3] for example the addition of nucleic acid amplification testing (e.g. GeneXpert)[4] and urinary lipoarabinomannan (U-LAM) testing for bacteriological confirmation of TB.[1] Other changes are necessary to address practical implementation challenges that become evident as definitions are applied over time, in different contexts. A case in point would be decreasing the number of consecutive cultures required for bacteriologically-confirmed cure in drug-resistant TB (DR-TB) from 5 to 3.[1] In general, a pragmatic approach is required for definitions to be applicable in a wide range of programmatic settings while being clinically meaningful and scientifically accurate. The latest major revision of the *Definitions and reporting framework was* published in 2013, with minor updates in 2014 and 2020.[1]

Shorter regimens lasting 9 - 11-months are now standard of care for most patients with uncomplicated DR-TB.[5] The 'BPaL' regimen, recommended in specific complicated scenarios, is of 6 - 9-months duration and no longer has a distinct intensive and continuation phase.[5,6] With such short regimens, the timing of assessment of bacteriological response to guide subsequent treatment also occurs earlier (at 4 - 6 months) compared with traditional long regimens (at 6 - 8 months). Injectable agents have largely been replaced by new and repurposed oral drugs. With several novel drug candidates and regimen combinations in various stages of testing, similar changes are expected to occur, and are likely to also apply to drug-susceptible TB (DS-TB) in future.[7,8] Similarly, the use of individualised rather than standardised regimens, which is currently the standard of care in well-resourced, low-burden settings, are likely to become more common.[9] In these scenarios, several aspects of the 2013 definitions are no longer directly applicable. Additionally, while different outcome definitions for DS-TB and DR-TB may be necessary, given the differences in clinical management at present, it may indeed be simpler if a single set of outcome definitions could be applied to both types of disease.

With these considerations in mind, several authors have proposed alternative outcome definitions applicable to shorter and individualised DR-TB regimens in recent years.[3,10,11] The Tuberculosis Network European Trials (TBNET) group propose a 'simplified' definition for cure, based on a negative-culture status at 6 months and no subsequent positive-culture for up to a year post-treatment. This minimises culture requirements for cure or failure, but necessitates a one-year post-treatment follow-up period. Feasibility concerns in high-burden settings has precluded the WHO from making post-treatment follow-up a requirement for programmatic evaluation, despite it being required in clinical trials and other research settings. The TBNET definitions also avoid any reference to distinct treatment phases or specific drugs (the 2013 WHO definitions still list acquired resistance to injectable agents or quinolones as a reason for failure).[10,12]

In November 2020, the WHO convened a stakeholder meeting to revise TB outcome definitions.[13] The primary focus was on changes in the DR-TB treatment landscape, but DS-TB outcome definitions were also revised during the meeting. These definitions, published as part of the meeting report, were intended for use from 2021, although the *Definitions and reporting framework for tuberculosis* has not yet been updated at the time of writing. The new definitions represent a major revision with several key changes, including:

- Full harmonisation of DS-TB and DR-TB outcome definitions; the only difference being the measure for bacteriological response which is still smear and/or culture in DS-TB, but culture only in DR-TB.
- No specified timing for the assessment of bacteriological response and no references to specific treatment phases or specific drugs.
- Loosened criteria for bacteriologically confirmed cure (e.g. in DR-TB, bacteriological response now requires only 2 consecutive negative cultures taken ≥7 days apart; previously, 3 consecutive negative cultures taken ≥30 days apart were required for cure).
- A new, optional outcome category called 'sustained treatment success' based on a post-treatment follow-up period to ascertain disease-free survival in settings where this is feasible.

Some changes will affect a subset of frequently occurring 'special cases.' Cases without bacteriologically-confirmed disease (particularly relevant in children), can now be declared as 'treatment failed' based on inadequate clinical response. For DR-TB, the wording of death and loss to follow-up now also explicitly includes the period from diagnosis to start of treatment, which was previously not the case. An important concept regarding DR-TB outcomes that remains incompletely defined is 'regimen change.' Though it remains the basis for declaring treatment failure, exactly how to define regimen change will depend on the specific regimen. Stakeholders at the meeting argued that regimen change should indicate '*a change to a new regimen option or treatment strategy, rather than a change in individual drugs*' noting that '*some treatment regimens allow certain drug changes*.' Details are expected to follow in the updated *Definitions and reporting framework* and relevant chapters of the WHO operational handbook.[5]

The paper by Anderson *et al.*[14] in this issue of the *AJTCCM* underscores the importance of carefully and clearly worded standardised outcome definitions by demonstrating how different definitions can lead to markedly different results. The authors compared treatment outcomes using 2013 WHO-based and TBNET-based definitions in a retrospective cohort of DR-TB patients. Treatment occurred between 2008 and 2017 in a programmatic setting in Cape Town, South Africa, using mostly injectable-containing standardised regimens. Bedaquiline was largely unavailable at the time. The study included inpatients from a specialist DR-TB hospital selected for folder review based on having undergone serial drug susceptibility testing (DST) during treatment. Repeated DST is typically done for inadequate clinical or bacteriological

response or following treatment interruption. The cohort therefore represents a group of patients selected for having complicated treatment histories with 88% of the cohort found to have acquired additional resistance after treatment initiation.

Very few of the 246 included patients achieved a favourable outcome with the initial DR-TB regimen (3 patients using WHO definitions v. 6 patients using TBNET definitions). Most patients required treatment with more than one DR-TB regimen and consequently, the authors assigned multiple serial outcomes to most patients. When considering the outcome for the final (most recent) regimen for each patient, the proportion with cure and treatment failure was considerably different between the two sets of definitions: cure was assigned in 9% v. 3% and treatment failure in 22% v. 42% for WHO v. TBNET definitions, respectively. Assigning multiple outcomes to a single patient arises from the retrospective nature of this study. With prospective application, these patients would be assigned a single outcome of failure, which precludes any other outcome assignment at a later point,[2] irrespective of the outcome of subsequent treatment strategies. This scenario was discussed by stakeholders during the 2020 meeting and the view supported by most was *'that failure should be assigned to a specific regimen rather than to a patient, who might have more than one disease episode or might receive different treatment regimens.*'[15] It has previously been suggested that such patients should be re-entered into the register as retreatment cases, but this approach will artificially inflate case numbers.[15] The study further highlights practical challenges when definitions are applied strictly as worded to the logistical variations seen in programmatic settings. For example, 'monthly' sputum collection visits occurring slightly less than 30 days apart are problematic for the 2013 WHO definition of cure which requires samples to be at least 30 days apart. Similarly, culture status at 6 months was clarified with the TBNET investigators as being between 154 and 182 days, which the authors argued should be extended even wider. However, with implementation of the new WHO definitions, both these issues will be rendered obsolete.

Though the treatment outcomes reported in their study are largely of historic significance due to the older regimens used, it contributes valuable insights regarding practical challenges with consistent application of standardised outcome definitions. The revised WHO definitions are a bold step aimed at simplifying and future-proofing TB outcome definitions in an era of shorter and possibly more individualised therapy. It also unifies the definitions for DS-TB and DR-TB and resolves some recognised implementation issues with the 2013 definitions. However, the full effect of the new definitions will become clear only once implementation starts. Ongoing research is required to determine the impact of the new definitions on programmatic outcomes and to understand how these new criteria perform in a wide range of programmatic and research contexts.

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1. World Health Organization. Definitions and reporting framework for tuberculosis (2013 revision, updated December 2014 and January 2020). https://www.who.int/publications/i/item/9789241505345 (accessed 5 March 2022).
2. Günther G, Heyckendorf J, Zellweger JP, et al. Defining outcomes of tuberculosis (Treatment): From the past to the future. Respiration 2021;100(9):843-852. https://doi.org/10.1159/00051639
3. Migliori GB. Evolution of programmatic definitions used in tuberculosis prevention and care. Clin Infect Dis 2019;68(10):1787-1789.
4. World Health Organization. Rapid implementation of the Xpert MTB/RIF diagnostic test. Technical and operational 'how to' - practical considerations. http://whqlibdoc.who.int/publications/2011/9789241501569_eng.pdf. 2011. (accessed 29 February 2022).
5. World Health OrganiZation. WHO Consolidated Guidelines on Tuberculosis, Module 4: Drug-Resistant Tuberculosis Treatment. 2020 (accessed 3 March 2022).
6. Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med 2020;382(10):893-902. https://doi.org/10.1056/nejmoa1901814
7. Dorman SE, Nahid P, Kurbatova EV, et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. N Engl J Med 2021;384(18):1705-1718. https://doi.org/10.1056/nejmoa2033400
8. Turkova A, Wills GH, Wobudeya E, et al. Shorter treatment for nonsevere tuberculosis in African and Indian Children. N Engl J Med 2022;386(10):911-922. https://doi.org/10.1056/nejmoa2104535
9. Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med 2019;200(10):e93-e142. https://doi.org/10.1164/rccm.201909-1874st
10. Gunther G, Lange C, Alexandru S, et al. Treatment outcomes in multidrug-resistant tuberculosis. N Engl J Med 2016;375(11):1103-1105. https://doi.org/10.1056/NEJMc1603274
11. Schwoebel V, Chiang CY, Trébucq A, et al. Outcome definitions for multidrug-resistant tuberculosis treated with shorter treatment regimens. Int J Tuberc Lung Dis 2019;23(5):619-624. https://doi.org/10.5588/ijtld.18.0798
12. Gunther G, van Leth F, Alexandru S, et al. Clinical management of multidrug-resistant tuberculosis in 16 European countries. Am J Respir Crit Care Med 2018;198(3):379-386. https://doi.org/10.1164/rccm.201710-2141oc
13. World Health Organization. Meeting report of the WHO expert consultation on drug-resistant tuberculosis treatment outcome definitions (Nov 2020). 2021. (accessed 3 March 2022).
14. Anderson K, Pietersen E, Dheda K, van der Heijden YF. Comparison of treatment outcome definitions in drug-resistant tuberculosis patients with high incidence of acquired second-line drug resistance. Afr J Thoracic Crit Care 2022;28(2):59-65. https://doi.org/10.7196/AJTCCM.2022.v28i2. 177
15. Laserson KF, Thorpe LE, Leimane V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2005;9(6):640-645.

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