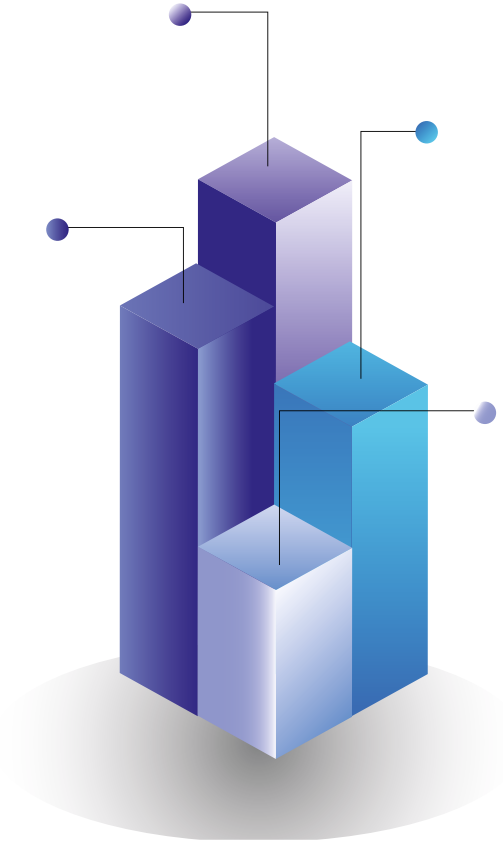
Meeting report of the WHO expert consultation on drug-resistant tuberculosis treatment outcome definitions

17-19 November 2020



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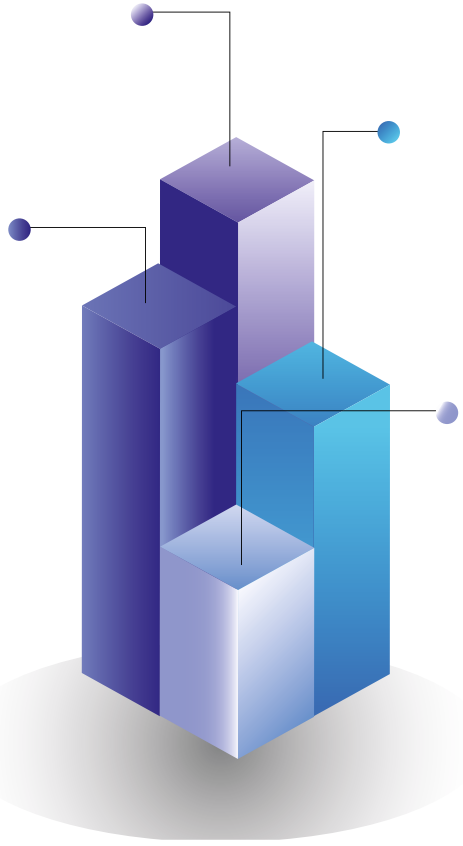

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Contents

Abbreviations

ADR	adverse drug reaction
AIDS	acquired immunodeficiency syndrome
BPaL	bedaquiline, pretomanid and linezolid
DNA	deoxyribonucleic acid
DR-TB	drug-resistant tuberculosis
DST	drug-susceptibility testing
DS-TB	drug-susceptible tuberculosis
HIV	human immunodeficiency virus
MDR/RR-TB	multidrug-resistant or rifampicin-resistant tuberculosis
MDR-TB	multidrug-resistant tuberculosis
NTP	national tuberculosis programme
RNA	ribonucleic acid
RR-TB	rifampicin-resistant tuberculosis
TB	tuberculosis
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Executive summary

The World Health Organization (WHO) held an online consultation on the definitions of drug-resistant tuberculosis (DR-TB) treatment outcomes, on 17–19 November 2020. Organized by the WHO Global TB Programme, Geneva, Switzerland, the consultation was attended by 66 participants, representing countries, bilateral and multilateral agencies, international organizations, nongovernmental organizations, civil society and academia.

The consultation discussed recent and potential future developments in treatment regimens for both DR-TB and drug-susceptible TB (DS-TB) and considered possible changes to the treatment outcome definitions needed for programmatic monitoring. The specific objectives of the consultation were to discuss:

- recent developments in treatment regimens and in diagnostics for monitoring treatment of DR-TB, and to determine how these developments affect the current definitions of treatment outcomes; and
- options for changing the treatment outcome definitions, including the pros and cons of these options from various perspectives (e.g. clinical, programmatic and surveillance).

The online consultation ran for a total of 9 hours, with a 3-hour session on 3 consecutive days. Most of the time was devoted to discussion of four topics:

- recent developments in tuberculosis (TB) treatment and diagnostics for treatment monitoring;
- principles and strategic issues that will underlie the new definitions of treatment outcomes;
- operational issues related to the definitions of treatment outcomes; and
- an outline of the new definitions of treatment outcomes, including next steps.

Before the meeting, the WHO Global TB Programme shared a concept note with participants for review and feedback. The note provided overviews of the history of definitions of treatment outcomes and of recent developments in TB treatment and diagnostics for treatment monitoring. It also provided a rationale for potential changes in the definitions of treatment outcomes, with the main reasons for changes being that:

- recent DR-TB treatment regimens are shorter, whereas the current definitions are mainly applicable to longer regimens;
- the all-oral nature of recommended regimens departs from the traditional intensive and continuation phases, whereas the current definitions include timing of culture conversion;
- expected treatment response thresholds occur earlier with new combinations of medicines, whereas the current definitions link assessment to bacteriological conversion; and
- there is still no reliable, suitable and universally applicable biomarker for treatment follow-up and monitoring; thus, a clear definition of bacteriological conversion and reversion is needed to inform the treatment regimen (i.e. whether to continue, halt or modify it).

The difference in treatment outcome definitions for DR-TB and DS-TB is also considered a challenge for implementation. Hence, it would be ideal to have a simplified set of treatment outcome definitions, applicable to both DR-TB and DS-TB.

The concept note proposed three options for outcome definitions to be discussed at the consultation. Options 1 and 2 related to DR-TB treatment outcomes only, whereas option 3 was applicable to both DR-TB and DS-TB.

During the consultation, participants identified general principles that are important and relevant to the revision of treatment outcome definitions, and suggested that the revised definitions will need to:

- be simple and, if possible, applicable to treatment of both DS-TB and DR-TB;
- be applicable to treatment regimens of different lengths;
- de-emphasize the traditional division between intensive and continuation phases;
- identify the appropriate threshold for bacteriological conversion (or reversion) in relation to the definitions of "treatment failed", "cured" and "treatment completed";
- consider the use of appropriate diagnostics for treatment monitoring;
- have clear parameters for defining treatment failure, based on a decision to change or stop treatment, or reliable evidence for non-response; and
- be practical for clinical and programmatic monitoring, and feasible for national TB programmes (NTPs) to implement.

The consultation highlighted the following strategic issues, which should guide the development of new treatment outcome definitions:

- Harmonization of treatment outcomes for DS-TB and DR-TB is needed, although some peculiarities and specifics should remain (e.g. treatment monitoring by sputum culture for DR-TB and by sputum microscopy for DS-TB).
- Despite some distinct phases remaining in current regimens, the overall trend is towards monotonous regimens. Thus, linking definitions to treatment phases should be avoided, which means that the time threshold to declare cure or treatment failure should be revised.
- While considering new treatment monitoring tools, we will continue to rely on the available tools (i.e. sputum culture for DR-TB and sputum microscopy for DS-TB), despite their drawbacks.
- At the end of treatment, it is important and feasible for programmes to ascertain cure. The idea of sustained cure may have value, but perhaps only in operational research, depending on needs and the resources available.

Participants spent some time discussing proposed definitions of the treatment outcome categories: "treatment failed", "cured", "treatment completed", "died", "lost to follow-up" and "not evaluated". Discussion focused on Option 3 – definitions of treatment outcomes that apply to both DR-TB and DS-TB.

The consultation led WHO to propose new definitions of TB treatment outcomes that apply to assessment of treatment outcomes of both DS-TB and DR-TB, as summarized in the box below.

Proposed new treatment outcome definitions

Treatment failed
A patient whose treatment regimen needed to be terminated or permanently changed[a] to a new regimen or treatment strategy.

Cured
A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response[b] and no evidence of failure.

Treatment completed
A patient who completed treatment as recommended by the national policy, whose outcome does not meet the definition for cure or treatment failure.

Died
A patient who died[c] before starting treatment or during the course of treatment.

Lost to follow-up
A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

Not evaluated
A patient for whom no treatment outcome was assigned.[d]

Treatment success
The sum of cured and treatment completed.

An optional definition proposed for use in operational research only

Sustained treatment success
An individual assessed at 6 months (for DR-TB and DS-TB) and at 12 months (for DR-TB only) after successful TB treatment, who is alive and free of TB.

[a] Reasons for the change include:
- no clinical response and/or no bacteriological response (see note 'b');
- adverse drug reactions; or
- evidence of additional drug resistance to medicines in the regimen.

[b] "Bacteriological response" refers to bacteriological conversion with no reversion.
- "bacteriological conversion" describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are negative.
- "bacteriological reversion" describes a situation where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.

[c] Patient died for any reason.

[d] This includes cases "transferred out" to another treatment unit and those whose treatment outcome is unknown; however, it excludes those lost to follow-up.

Updated definitions will be issued by WHO and will be included in the 2021 revision of WHO's *Definitions and reporting framework for tuberculosis*. The definitions will also need to be adopted for programmatic implementation, and for use in registration and reporting to monitor progress towards ending TB.

1. Background

1.1. Introduction and history

Monitoring treatment of tuberculosis (TB) is critically important in clinical practice, to ensure cure and to prevent failure and relapse. Standardized treatment outcome definitions for TB have been a feature of World Health Organization (WHO) policies and national TB surveillance systems for many years, and have allowed monitoring of TB treatment outcomes over time at national and global levels. Currently, treatment success – for patients with drug-susceptible TB (DS-TB) or with drug-resistant TB (DR-TB) – is one of the top 10 indicators in WHO's End TB Strategy, with a target of at least 90% *(1)*. High coverage of appropriate treatment is considered a fundamental requirement for achieving the milestones and targets of the End TB Strategy.

Although treatment outcome definitions for DS-TB have been in place for several decades, outcome definitions for multidrug-resistant TB (MDR-TB) were first proposed in 2005 *(2)*. The development of MDR-TB treatment outcome definitions was based on the definitions for DS-TB in use at the time *(2, 3)*, a review of definitions for MDR-TB in the medical literature, and extensive discussions among key stakeholders over 2 years. Representatives from several DOTS-Plus[1] projects were involved in this consultation, providing important contextual information on the application of these definitions at the country level. The outcome of this process was a set of definitions for both MDR-TB case registration and treatment outcomes. The MDR-TB treatment outcome definitions included six mutually exclusive definitions that were "designed to fit the wide range of treatment regimens and durations currently in use worldwide"; the definitions were also said to "rely on the use of laboratory culture as a monitoring tool" *(2)*. These definitions are given in Annex 1, as are the MDR-TB treatment outcome definitions adopted and published by WHO in 2006 *(4)*. These definitions carried over to WHO's 2008 guidelines on the programmatic management of TB; the definitions were largely unchanged, with a brief qualifying statement on interruption of TB treatment for people who had the treatment outcome of "defaulted", noting that this interruption was not for medical reasons *(5)*.

In 2009, Chiang et al. proposed a revised definition for treatment failure *(6)*, arguing that the WHO definition of "failed" could not be used *prospectively* to guide the clinical management of MDR-TB, because it did not indicate at which month of treatment failure should be declared in cases where the patient remained sputum smear positive. Chiang et al. also argued that the definition of "failed" did not consider modifications of the treatment regimen. They proposed that "failed" be defined as sputum culture positive after *n* months of treatment; they also suggested that this method of classification could be used to guide the clinical management of MDR-TB patients.

A short time later, the International Union Against TB and Lung Disease convened an internal task force of consultants to address the definition of treatment failure for patients with MDR-TB. Revised outcome definitions were proposed in a 2011 paper *(7)* that introduced the concepts of change of the regimen, bacteriological conversion and reversion, and adverse events. The authors noted that these definitions required further research if they were to be validated.

[1] DOTS-Plus is an initiative for managing MDR-TB. It is based on the five elements of the directly observed treatment short course (DOTS) strategy. DOTS-Plus considers specific issues (e.g. use of second-line anti-TB drugs) that need to be addressed in areas where there are high levels of MDR-TB.

1.2. Pre-2021 treatment outcome definitions for DR-TB and DS-TB

In 2013, WHO published an updated definitions and reporting framework for TB, which was further updated in 2014 and in 2020 *(8)*. That document presents the current treatment outcome definitions for both DR-TB and DS-TB.

The treatment outcome definitions for rifampicin-resistant TB (RR-TB) – including MDR-TB and extensively drug-resistant TB (XDR-TB) – are outlined in Table 1.1 and Annex 3. The treatment outcome definitions for DS-TB are given in Table 1.2 and Annex 1, for comparison with the historical and current treatment outcome definitions for DR-TB.

Table 1.1. *Pre-2021 definitions of treatment outcomes recommended by WHO for patients with RR-TB, MDR-TB and XDR-TB treated using second-line treatment regimens*

Outcome	Definition
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[a]
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[a]
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: – lack of conversion[b] by the end of the intensive phase;[a] or – bacteriological reversion[b] in the continuation phase after conversion[b] to negative; or – evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs; or – adverse drug reactions.
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown.)
Treatment success	The sum of cured and treatment completed.

MDR-TB: multidrug-resistant TB; RR-TB: rifampicin-resistant TB; TB: tuberculosis; XDR-TB: extensively drug-resistant TB.
[a] For "treatment failed", lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of the intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested, to determine when the criteria for "cured", "treatment completed" and "treatment failed" start to apply.
[b] The terms "conversion" and "reversion" of culture are defined here as follows: **conversion (to negative)** – culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion; **reversion (to positive)** – culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are positive. For defining "treatment failed", reversion is considered only when it occurs in the continuation phase.

With the current update to the definitions, several changes were introduced. The treatment outcome definitions of "cured" and "treatment failed" in MDR-TB cohorts were simplified to make them more widely applicable to patients who are still on treatment. These definitions could be defined prospectively and would no longer need to be assigned at the end of treatment. The treatment

outcome “defaulted” was changed to “lost to follow-up”, to better reflect reality and avoid the use of stigmatizing language *(8)*.

Since the publication of the WHO 2013 definitions and reporting framework for TB, various alternative definitions of the DR-TB treatment outcomes have been proposed. Suggestions (summarized in Annex 2) have included:

- revised definitions of “cure” and “treatment failure”, including an additional criterion for “treatment failure” based on sputum smear microscopy, and an option for the outcome of “cure” that includes a follow-up visit at 6 months after completion of treatment *(9)*;
- treatment outcomes that consider a follow-up period after treatment ends *(10-12)*; and
- separate identification of drug resistance acquired during and after treatment, as part of the definition of “cure”, and consideration of evidence of acquired resistance to fluoroquinolones or injectables (or of adverse drug reactions [ADRs] to these drugs) as not necessarily implying treatment failure *(13)*.

Several clinical trials of shorter regimens for MDR/RR-TB have been conducted since the 2013 publication of the WHO definitions and reporting framework for TB *(8)*. In many of these trials, the primary outcome measures included at least one TB treatment outcome. Annex 3 summarizes the treatment outcome definitions from selected trials that feature shorter regimens for DR-TB. Although trial participants are often recruited in the context of a country’s national TB programme (NTP), trial conditions usually include additional support and follow-up of patients to ensure controlled conditions and treatment adherence, which may not routinely be available in the programmatic setting. This may affect the feasibility of these treatment outcome definitions outside trial settings. Nonetheless, it can be helpful to assess the definitions used in recent clinical trials, and to compare their end-points with the end of treatment outcomes as defined by WHO for routine programme monitoring. In trials and other studies where MDR/RR-TB treatment is being shortened, it is particularly important to consider follow-up after treatment ends, when assigning outcomes to determine the durability of treatment success and to compare outcomes with those on regimens of longer duration.

Table 1.2. *Pre-2021 definitions of treatment outcomes recommended by WHO for patients with DS-TB treated using first-line treatment regimens*

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear or culture negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who dies for any reason before starting or during the course of treatment.
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

Outcome	Definition
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of cured and treatment completed.

DS-TB: drug-susceptible TB; TB: tuberculosis; WHO: World Health Organization.

1.3. Advances in treatment of TB and diagnostics for treatment monitoring

1.3.1 Recent developments in the treatment of DR-TB

DR-TB treatment regimens have changed since the WHO definitions and reporting framework was published in 2013 *(8)*. These changes have direct relevance for the treatment outcome definitions for patients with MDR/RR-TB and XDR-TB.

In 2016, WHO for the first time recommended a standardized shorter MDR-TB regimen (9–12 months) for eligible patients. This recommendation was updated in 2018 and in 2020 as evidence from studies and programmatic settings became available. In the latest WHO consolidated guidelines on treatment of DR-TB, the shorter, all-oral regimen is the preferred option for eligible patients *(14)*; hence, the use of shorter regimens is likely to increase in coming years. Currently, about 40% of countries that reported data to WHO in 2020 are providing shorter regimens for patients with MDR/RR-TB[2]. The duration of these regimens can be as short as 9 months; thus, any MDR-TB treatment outcome definitions would need to be used within this comparatively short time frame.

The longer regimens, defined as those that are used for treatment of MDR/RR-TB, **last 18 months or more** and are designed using hierarchy of recommended medicines to include a minimum number of medicines considered to be effective based on drug-resistance patterns or patient history will remain in use *(14)*. Therefore, any DR-TB treatment outcomes should be applicable to patients receiving either longer or shorter regimens.

Another issue is that regimens for MDR/RR-TB and even for XDR-TB could become even shorter. This is exemplified in the BPaL regimen[3] for patients with MDR-TB and additional fluoroquinolone resistance, which is recommended by WHO for use under operational research conditions. This 6-month regimen is extendable to 9 months for patients who missed doses, remained culture positive or reverted from culture negative to positive between months 4 and 6 of treatment.

Since 2018, WHO guidelines have also recommended a 6-month regimen [6(H)RZE-Lfx] for treatment of rifampicin-susceptible isoniazid-resistant TB *(14)*.

1.3.2 Recent and potential future developments in the treatment of DS-TB

The standardized 6-month first-line treatment regimen for DS-TB (2HRZE/4HR) has remained the same for many years, although the 8-month regimen for previously treated TB cases (known as the Category 2 regimen) was phased out in 2017 *(15, 16)*. The duration of the treatment regimen for DS-TB has reduced to 4 months based on results from well-designed clinical trials. One study (Study 31) showed that a 4-month regimen containing rifapentine and moxifloxacin (2HPZM/2HPM)

[2] Based on preliminary data reported to WHO in 2020, where 88 countries have reported using shorter regimens for MDR/RR-TB and 82 have reported using all-oral regimens for MDR/RR-TB.

[3] The BPaL regimen contains bedaquiline, pretomanid and linezolid in combination. Pretomanid is a new compound (a nitroimidazole). In April 2019, pretomanid received approval from the United States Food and Drug Administration (US FDA) to be used in combination with bedaquiline and linezolid.

met non-inferiority criteria in comparison with the standardized regimen (2HRZE/4HR) *(17)*. Another study (SHINE) found that 4-month treatment (2HRZE/2HR) was as effective as the standard 6-month treatment for children with minimal TB *(18, 19)*. Although these shortened regimens have not been properly assessed by a WHO guideline development group, the study results are encouraging and show the potential for DS-TB to be treated effectively using regimens with a duration of less than 6 months, which may be recommended for implementation in future.

1.3.3 Updates on TB diagnostics for treatment monitoring

There has been progress in TB diagnostics, with several new assays that show potential for monitoring treatment or assessing treatment outcomes. However, overall, the TB community still lacks a reliable, suitable and universally applicable biomarker for treatment follow-up and monitoring. The current WHO recommendation on monitoring for MDR/RR-TB patients on longer or shorter regimens is performance of sputum culture in addition to sputum smear microscopy, to monitor the treatment response. Ideally, sputum culture should be repeated at monthly intervals (strong recommendation, moderate certainty in the estimates of test accuracy) *(14)*.

Although microscopy is included in the current reporting framework, sputum smear alone lacks sensitivity and is not informative about the viability of the identified bacteria (i.e. the bacilli found by smear microscopy may be dead). Conversely, genotypic or molecular tests may be insufficiently specific because they can generate positive results even after successful completion of treatment *(20)*, and they cannot provide an indication of the viability of the bacilli or active disease (this applies to DNA-based tests; to date there are no RNA-based tests). Culture is the only test that can detect the viability of the identified pathogen but potential issues with implementing culture include feasibility, quality assurance, turn-around time and access.

It is difficult to comprehensively assess for recurrence in all those who complete their treatment successfully, owing to the lack of a suitable biomarker of TB disease activity, combined with the low likelihood that people who stay healthy after completing their treatment would want to continue follow-up for years after treatment.

1.4. Rationale for the change

There are several reasons for changing the definitions of treatment outcome, especially in relation to MDR/RR-TB patients, as outlined below.

One challenge for use of the current treatment outcome definitions for DR-TB is that treatment regimens for MDR/RR-TB of a shorter duration (the 9–12 month all-oral shorter regimen or the 6–9 month BPaL regimen) have been introduced along with the longer regimens (18–20 months), whereas the current definitions of treatment outcomes for MDR/RR-TB apply mainly to the longer regimens.

Another issue is that current recommended treatment regimens for DR-TB – whether shorter or longer – are predominantly all-oral. These regimens no longer have the traditional specific intensive or continuation phases, and this situation is likely to persist well into the future. In the current DR-TB treatment outcome definitions, the definitions of “cured”, “treatment completed”, “failed” and, by default, “treatment success” all incorporate an aspect of timing of culture conversion that is related to the intensive phase. Given that many future regimens will not have an intensive phase as such and will not contain injectables, DR-TB treatment outcome definitions that depend on events in specific phases will no longer make sense.

As more effective combinations of medicines are used to treat DR-TB, earlier bacteriological conversion from positive to negative (by sputum smear microscopy or culture) may mean that the expected threshold of bacteriological conversion needs to be revised in definitions of DR-TB treatment outcomes. In the current definitions, conversion from positive to negative (or reversion from culture negative to positive) is included in the definitions of “cured”, “treatment completed” and

"treatment failed" (and, by definition, "treatment success"). This is usually linked to the division of treatment into phases, or to the timing between cultures (i.e. 30 days); however, the use of more effective drug combinations and the shorter duration of regimens (in clinical research and in practice) may lead to earlier sputum and culture conversion. Other recent programmatic developments may also limit the continued relevance of bacteriological conversion based on sputum microscopy; for example, the earlier detection of TB infection using rapid molecular diagnostics without a microscopy result (because of unavailability of microscopy or early stage of disease).

A further challenge is that the definition of "treatment failed" has typically signalled that a patient needs to stop TB treatment and be provided with a new and more effective regimen, guided by drug-susceptibility testing (DST). For example, the current definition of "treatment failure" for patients with DS-TB would usually mean that the patient needs to stop treatment and be started on a new regimen that is generally designed for treatment of MDR/RR-TB. Similarly, the current definition of "treatment failure" for patients with MDR/RR-TB includes a component linked to the past definition of XDR-TB (i.e. "evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs" *(8)*). The definition of XDR-TB has recently been updated, following a consultation in late 2020 *(21)*, and the new definition may need to be incorporated into the "treatment failed" definition. As individualized second-line regimens have become more widely available, programmes are increasingly using the "treatment failed" definition to decide when a regimen needs to be modified, but this comes at the expense of having a uniform microbiological end-point (as used in trials). Thus, two individuals with an identical clinical picture may not both be classified as "treatment failure" if they are in settings that differ in their capacity to offer effective treatment alternatives. Hence, there may be a need for an additional, optional set of outcome definitions for programmes that can monitor patients prospectively and beyond the completion of treatment (leading to the next point).

The current treatment outcome definitions are different for DR-TB and DS-TB, causing challenges for implementation at the programme level. It would be preferable to have a simplified set of treatment outcome definitions that apply to both DS-TB and DR-TB, which would simplify implementation in clinical and programmatic monitoring, and surveillance.

In addition, there have been calls in the literature to define treatment outcomes for patients with MDR/RR-TB sometime after the end of treatment rather than at the end of treatment. This is also a feature of some clinical trials, especially those where the period of treatment has been shortened to ensure that patients are treated effectively and do not relapse. Although it may be prudent for clinicians to follow up patients after treatment ends, it might be difficult for all NTPs to follow up all patients after treatment finishes. In addition, many countries lack population-level coverage with a personal unique identifier that is accessible at the point of care, making it difficult to complete the registration of people who relapse or die of TB, especially in places where TB care is diversified and no reliable mortality statistics are kept. With this approach, there would also be a risk that treatment outcomes are not assigned promptly. Thus, the definitions should consider the capacity of the NTP to follow up and evaluate patients during and after their treatment *(22)*.

1.5. Consultation objectives

Various programmatic developments since the 2013 WHO definitions and reporting framework *(8)* have direct relevance for the monitoring of treatment outcomes for patients with MDR/RR-TB and DS-TB. Hence, there is a need to make the definitions of treatment outcomes applicable to all patients, all treatment regimens and all approaches.

The consultation aimed to discuss recent and potential future developments in treatment regimens for both DR-TB and DS-TB, and to consider possible changes of treatment outcome definitions required for programmatic monitoring. Updated outcome definitions will be included in the 2021 revision of the definitions and reporting framework.

The specific objectives of the consultation were to discuss:

- recent developments in treatment regimens and in diagnostics for monitoring treatment of DR-TB, and to determine how these developments affect the current definitions of treatment outcomes; and
- options for changing the treatment outcome definitions, including the pros and cons of these options from various perspectives (e.g. clinical, programmatic and surveillance).

2. Summary of the consultation

2.1. Setting the scene for the consultation

Before the meeting, the WHO Global TB Programme shared a concept note with participants for review and feedback. The note provided overviews of background and history of definitions of treatment outcomes, rationale for changes and some possible options for new definitions. Several participants also reviewed and provided feedback on the concept note before the meeting; their feedback was incorporated in a revised note, and a summary of the feedback and revised definition options was presented at the meeting.

The consultation comprised three online meetings held via Zoom over three consecutive afternoons (see Annex 4 for the agenda). The participants (listed in Annex 5) reflected a diverse range of stakeholders and end users from relevant sectors, including representatives from high TB and MDR-TB burden countries, NTP managers, clinicians, researchers, academics, donors, partner technical organizations, civil society and other WHO departments. Declarations of interest were sought from selected participants according to the requirements of WHO's guidelines for declaration of interests.

To supplement the information in the concept note, the first session included four brief presentations that provided background information relevant to the current and possible future definitions of TB treatment outcomes. The remainder of the meeting was devoted to discussion.

Dr Tereza Kasaeva (Director, WHO Global TB Programme) opened the meeting by welcoming all participants and thanking them for their interest in the consultation. She emphasized the need for an update of the definitions of TB treatment outcomes, given developments in the treatment regimens of DR-TB and DS-TB since the 2013 update of the WHO definitions and reporting framework *(8)*. In particular, the introduction of shorter MDR-TB regimens (of 6 or 9 months duration) and the transition from injectable-based regimens to all-oral regimens highlight the need to make these definitions applicable to all situations and all treatment regimens, including for patients with MDR/RR-TB. The updated definitions will become part of the planned 2021 revision of the WHO definitions and reporting framework.

Dr Fuad Mirzayev (WHO Global TB Programme) outlined the current situation and progress in the management of MDR/RR-TB, including gaps in case detection, treatment enrolment and treatment outcomes. He showed how DR-TB treatment outcome definitions have evolved as part of the definitions and reporting framework for TB, and with the evolution of the DR-TB treatment guidelines. Dr Mirzayev noted that the objective of the meeting was to discuss changes and necessary updates in the DR-TB treatment outcome definitions for programmatic monitoring. Such changes and updates are expected to address practical issues in relation to implementing the current recommended treatment regimens, while taking into consideration further developments in the treatment pipeline based on clinical trials, especially the tendency towards shortening the duration of TB treatment regimens. He also highlighted issues with current definitions.

Dr Morten Ruhwald (Foundation for Innovative New Diagnostics [FIND]) discussed the future of diagnostics for treatment monitoring and correlates of cure of TB, noting that current treatment monitoring relies mainly on the tools of culture and smear microscopy. Several new assays show potential for monitoring of treatment or correlate treatment outcomes, and this is a fast-moving field that is being accelerated by major drug development. The presentation highlighted the need for reliable and simple tools for treatment follow-up and monitoring, with characteristics such as fast time to result, high sensitivity and specificity, superior safety profile, high precision, low variability and potential for lower cost.

Dr Medea Gegia (WHO Global TB Programme) summarized general principles for the revision of treatment outcome definitions, feedback on the concept note, and options for revision of the definitions.

The feedback on the concept note included comments suggesting that it is still too early to combine treatment outcome definitions for DS-TB and DR-TB. However, most respondents opted for simplification and unification of definitions for both DS-TB and DR-TB, and for all registered TB cases (not just for those started on treatment). Most comments did not favour an additional definition, but there was support for introducing post-treatment outcomes at 6 or 12 months after the end of treatment. Several comments focused on the proposed changes for definitions of "cured", "failed" and "not evaluated"; the need for "bacteriological conversion" to favour culture rather than smear microscopy; and the need for definitions of "cured", "failed" and "treatment completed" to be applicable to clinically diagnosed TB cases, including TB in children. The secretariat reviewed all the feedback and incorporated it as far as possible in the revised definition options that were presented during the consultation.

In summary, participants' feedback highlighted the need for careful reassessment of the definitions of "treatment failed", "cured", "treatment completed", "bacteriological conversion" and "bacteriological reversion". Ideally, outcome definitions should be applicable to all registered patients, including DS-TB and DR-TB, adults and children, and bacteriologically and clinically diagnosed TB; and should be able to be used with both electronic and paper-based registration platforms that allow quarterly and annual reporting.

Dr Linh Nguyen (WHO Global TB Programme) summarized key challenges for updating the definitions of treatment outcomes, to facilitate the discussions in subsequent sessions. The challenges include:

- the wide range of length (6–18 months) of the recommended MDR-TB treatment regimens, whereas the current definitions are mainly applicable to longer regimens (18+ months);
- the shift from the use of mainly injectable-based regimens to all-oral regimens, without a clear distinction between the intensive phase and continuation phase – the definitions of "failed", "cured", "treatment completed" (and "treatment success") all incorporate an aspect of timing about culture conversion that relates to the intensive phase;
- the fact that the threshold for bacteriological conversion cannot be defined or linked to changes in the phases of treatment because of earlier conversion with the use of new medicines and variety in the duration of regimens;
- the use of diagnostics for treatment monitoring (culture and sputum microscopy):

  – sputum smear alone lacks sensitivity and is not informative about the viability of the identified bacteria;

  – there are implementation challenges for culture (e.g. limited access and delay in results);

  – the use of "diagnostic test" in treatment outcome definitions differs for DR-TB (culture) and DS-TB (microscopy);

  – a simplified set of treatment outcome definitions that applies to both DS-TB and DR-TB (Option 3) would be useful, but would need to specify tests for treatment monitoring;
- defining "treatment failure" requires multiple parameters to be considered (e.g. bacteriological conversion or revision, acquired drug resistance and ADRs); and
- timing for declaration of cure – there has been a call to define treatment outcome at a period after the end of treatment, to ensure that patients are effectively treated without relapse (i.e. relapse-free cure); however, operational issues may make it difficult for NTPs to follow up all patients after treatment finishes.

2.2. Proposed options for new definitions of TB treatment outcomes

The consultation discussed three options for outcome definitions; these options are given in full in Annex 6. In each option, reference to an intensive phase has been removed; also, the outcomes of "cured" and "treatment completed" are mutually exclusive, as are the definitions of "cured" and "treatment failed" (thus, changes to the definition of "cured" will affect those for "treatment completed" and "treatment failed"). Also, in all three options, the changes proposed are in the outcomes "treatment completed", "cured" and "treatment failed".

2.2.1 Option 1

Option 1 applies to DR-TB only. "Treatment failed" is defined as treatment that needs to be terminated or permanently changed. Examples of reasons for assigning this outcome include sputum smear or culture positive in the last month of treatment and on at least one previous occasion, acquired resistance to at least one medicine in the treatment regimen, or occurrence of an ADR severe enough to warrant discontinuation of a drug or regimen. The definition of "cured" states that a patient is cured if they are sputum smear or culture negative in the last month of treatment and on at least one previous occasion. The definition of "treatment completed" specifies that no sputum or culture results are available (to determine whether the patient is cured), either because tests were not done or results were not available. Option 1 could be problematic for the longer treatment regimens because a treatment outcome needs to be assigned at the end of treatment (including the outcome of "treatment failed" in cases with no ADRs and no acquired resistance); however, clinicians may want to assign this outcome earlier and act accordingly.

2.2.2 Option 2

Option 2 also applies to DR-TB only and, again, "treatment failed" is defined as treatment that needs to be terminated or permanently changed. Examples of reasons for assigning this outcome include bacteriological conversion and reversion (defined based on culture only, and referring to having two consecutive negative cultures taken at least 30 days apart), acquired resistance to any medicines used in the regimen or ADRs. The definition of "cured" again specifies the patient population to which it applies, and includes a requirement for treatment completion and bacteriological conversion, with no evidence of treatment failure. The definition of "treatment completed" reflects treatment completion, but the outcome does not meet the definition for "cured" or "treatment failure".

2.2.3 Option 3

Option 3 is simpler because it applies to patients being treated for either DS-TB or DR-TB. The definitions of "treatment failed", "cured" and "treatment completed" are the same as those for Option 2. In the examples of reasons for assigning the outcome "treatment failed", the definitions of bacteriological conversion and reversion include both sputum smear (for DS-TB only) and culture (for both DR-TB and DS-TB).

2.3. Principles and strategic issues to guide the development of new definitions of treatment outcomes

The participants discussed general principles that are important and relevant to the revision of treatment outcome definitions. They agreed that the revised definitions will need to:

- be simplified and, if possible, applicable to treatment of both DR-TB and DS-TB;
- be applicable to treatment regimens of different lengths;

- de-emphasize the traditional division between intensive and continuation phases;
- identify the appropriate threshold for bacteriological conversion (or reversion) in relation to the definitions of "treatment failed", "cured" and "treatment completed";
- consider the use of appropriate diagnostics for treatment monitoring;
- have clear parameters for defining treatment failure, by a decision to change or stop treatment or by reliable evidence for non-response; and
- be practical for clinical and programmatic monitoring, and feasible for NTPs to implement.

Ideally, outcome definitions should be applicable to all registered patients, including DR-TB and DS-TB, adults and children, and bacteriologically and clinically diagnosed TB; should be able to be used with both electronic and paper-based registration platforms that allow quarterly and annual reporting; and be able to be assigned prospectively for prompt clinical decision-making. The definitions should also consider the capacity of NTPs to follow up and evaluate patients during treatment and after completion of treatment *(22)*.

Some key questions were raised on the strategic issues that guide discussions on the development of new treatment outcome definitions.

- Do we need new definitions for treatment outcomes?
- Do we want a common definition for both DR-TB and DS-TB?
- Should we consider longer and shorter regimens differently?
- Is it sufficient to use culture for DR-TB treatment monitoring and smear microscopy for DS-TB?
- Do we need to be specific about the timing of culture conversion?
- Do we need a definition for treatment outcome post-treatment?

The consultation highlighted strategic issues that should guide the development of new treatment outcome definitions:

- Harmonization of treatment outcomes for DS-TB and DR-TB is needed, although some peculiarities and specifics should remain (e.g. treatment monitoring by sputum culture for DR-TB and by sputum microscopy for DS-TB).
- Despite some distinct phases remaining in current regimens, the overall trend is towards monotonous regimens. Thus, linking definitions to treatment phases should be avoided, which means that the time threshold to declare cure or treatment failure should be revised.
- While considering new treatment monitoring tools, we will continue to rely on the available tools (i.e. sputum culture for DR-TB and sputum microscopy for DS-TB), despite their drawbacks.
- At the end of treatment, it is important and feasible for programmes to ascertain cure. The idea of sustained cure may have value, but perhaps only in operational research, depending on needs and the resources available.

2.4. Operational issues in relation to revision of the specific treatment outcome definitions

On days 2 and 3, participants discussed operational issues on the revision of definitions for each treatment outcome category: "treatment failed", "cured", "treatment completed", "died", "lost to follow-up" and "not evaluated". The discussion focused on the option for harmonized definitions of

treatment outcomes for both DS-TB and DR-TB.

2.4.1 Treatment failed

There were different opinions as to whether the new definition of "treatment failed" should be flexible or should include a list of situations when failure can be declared. A challenge here is how to define the regimen change, or "regimen terminated" or "permanently changed". Reasons for a regimen change may apply to specific regimens, to only DR-TB or DS-TB patients, or to only shorter or longer regimens. Some participants argued that details are needed to assist with implementation, and that new definitions should provide sufficient information to guide clinical practice and programmatic monitoring. If the definition of "treatment failed" is kept broad (e.g. as regimen change, but without details), it will offer little for clinical decision-making and its main use would be for reporting and recording purposes. Also discussed was whether a "treatment failed" definition should be assigned to the patient or to the regimen. Based on the original TB patient cohort analysis and reporting, most of the participants suggested 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 in different episodes.

Considering failure as a lack of cure, some participants suggested keeping the definition broad, simple and applicable to different regimens, with footnotes listing reasons for a regimen change. More details on the implementation, regimen-specific details (e.g. regarding duration and permitted treatment changes) and scenarios will be provided in the update to Module 4 of the WHO operational handbook *(23)*.

Participants highlighted the main reasons for a regimen change that should be defined as "treatment failed". Reasons included no response to treatment (bacteriologically or clinically), ADR or amplification of drug resistance, and various practical issues.

It was also noted that the "treatment failed" definition should be used to indicate a change to a new regimen option or treatment strategy, rather than a change in individual drugs. Some treatment regimens allow certain drug changes, and these should be outlined in the updated operational handbook.

"No response to treatment" is one of the most important reasons for treatment failure. It may be defined as no clinical response and/or no bacteriological response (i.e. lack of bacteriological conversion or evidence of bacteriological reversion).

"Bacteriological response" is defined as "bacteriological conversion with no reversion". The group suggested definitions of the bacteriological conversion and bacteriological reversion that could be used to support the definitions of "treatment failed" or "cured":

- "Bacteriological conversion" describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are negative.
- "Bacteriological reversion" describes a situation where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.

The clinical response is also important in monitoring treatment and defining "treatment failure", especially for extrapulmonary TB and childhood TB, where bacteriological evidence is not always available for confirming diagnosis or monitoring the treatment response. In practice, "no clinical response" may also imply an insufficient clinical response (defined by clinicians as lack of cure or failure of the prescribed treatment regimen).

Participants acknowledged that timing to determine no response to treatment (clinical or bacteriological response) should be defined according to the regimen. With the various durations of treatment regimens for DR-TB and DS-TB, adding timing thresholds to the definition may lead to inconsistency or limit the applicability of the definition for new regimens (which will soon be of < 6 months duration). The group suggested that regimen-specific timing to define "no response" needs to be clearly described in the updated operational handbook, and included in the revised definitions and reporting framework.

ADR was identified as another important reason for defining treatment failure. Although participants differed in their views on using ADR as a reason for failure, they acknowledged that, in practice, ADR is a common reason for termination or change of treatment regimen when it occurs with one or more drugs in the regimen. However, changing only one drug in the regimen (often due to ADR) should not be considered as regimen change, which should instead be defined according to the standardized or individualized treatment regimen. When a patient is on a standardized treatment regimen, regimen change implies a change of the whole regimen; in contrast, when a patient is on an individualized treatment regimen, regimen change implies a change of at least two drugs in the regimen. It was also suggested that, to keep the definition concise, these details should not be included in the definition of treatment failure, but should be featured in the update of Module 4 of the WHO operational handbook, and in relevant chapters of the definitions and reporting framework.

The detection of additional drug resistance to medicines in the regimen is evidence of treatment failure. Participants noted that the amplification of (or failure to detect) drug resistance normally leads to a lack of bacteriological conversion. Improved laboratory capacity for DST is important for monitoring of drug resistance at baseline and during the treatment course, especially for core drugs (e.g. rifampicin for DS-TB and fluroquinolones for MDR/RR-TB), but also for other new or repurposed drugs in Group A and Group B (e.g. bedaquiline, linezolid and clofazimine).

A practical issue about delay of the baseline DST result is that, if results arrive at a late stage of treatment and show resistance to one of the key drugs (e.g. rifampicin or fluroquinolone), a regimen change is required. Misclassification of disease type, driven by absence of initial data, which then leads to the patient being allocated to the wrong treatment regimen, should not be classified as failure. Another practical reason for a regimen change is stockout of medicines; again, this should not be classified as failure.

2.4.2 Cured

"Cured" is an outcome at the end of treatment that is used only for patients with bacteriologically confirmed pulmonary TB. The key features to define "cured" are completion of the treatment regimen, with evidence of bacteriological response (bacteriological conversion with no reversion) and no evidence of treatment failure. Patients with bacteriologically negative pulmonary TB and extrapulmonary TB cannot be defined as "cured" at the end of treatment owing to lack of evidence on bacteriological conversion during treatment or at the end of treatment; therefore, such patients can only be defined as "treatment completed" or other treatment outcomes rather than "cured".

Participants discussed the possibility of having a definition of "cured post-treatment", but acknowledged the importance of defining "cured" at the end of treatment and felt that the definition should be maintained. It was suggested that a new, optional definition of "sustained treatment success" could be used for operational research purposes and in programmes with this capacity; details of the discussion are provided in Section 2.4.7.

2.4.3 Treatment completed

Participants did not suggest major modifications to the proposed definition of "treatment completed" provided in Option 3. They noted that this treatment outcome is for patients who completed

treatment according to the national policy but whose treatment outcome did not meet the definition of "cured" (i.e. evidence of bacteriological response) or "treatment failure" (i.e. treatment regimen terminated or permanently changed). This definition can be applied to patients with pulmonary or extrapulmonary TB who were diagnosed without bacteriological confirmation.

To support the application and implementation of the definitions of "cured" and "treatment completed", participants suggested that the following definitions of pulmonary or extrapulmonary TB and a bacteriologically confirmed TB case should be featured in the updated operational handbook or relevant chapters of the definitions and reporting framework.

- Pulmonary TB refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as pulmonary TB because there are lesions in the lungs. Tuberculous intrathoracic lymphadenopathy (mediastinal or hilar, or both) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB.
- A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture or molecular WHO-recommended rapid diagnostic test (e.g. Xpert® MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started.
- Extrapulmonary TB refers to any bacteriologically confirmed or clinically diagnosed case of TB that involves organs other than the lungs (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, or meninges).

2.4.4 Died

Participants suggested defining "died" as a patient who died for any reason after TB diagnosis, whether before starting TB treatment or during treatment. In current treatment outcome definitions, death after diagnosis and before starting TB treatment is well reflected in the definition for DS-TB but not for DR-TB. An important gap in the programmatic implementation and in the registration and reporting systems is that patients with diagnosed TB who die before starting treatment are often not registered and notified. To close that gap, participants suggested that death before starting treatment should be included in the definition of "died", which would apply to both DR-TB and DS-TB.

2.4.5 Lost to follow-up

No change was proposed to the interruption for 2 consecutive months or more in the existing definition of "lost to follow-up" for both DR-TB and DS-TB. However, participants discussed including "lost to follow-up before starting treatment" (previously referred to as "initial defaulter") in the definition. The new definition addresses the inconsistency between current definitions of "lost to follow-up" for DR-TB and DS-TB, and may help NTPs to capture all patients lost to follow-up, including those lost before starting treatment and during treatment.

2.4.6 Not evaluated

Participants suggested that patients without any assigned treatment outcome or who do not meet any of the treatment outcome definitions ("cured", "completed", "failed", "died" and "lost to follow-up") should be defined as "not evaluated", which also implies that data on treatment outcome are missing or unknown. In addition, "not evaluated" includes patients who were "transferred out" to another treatment unit and whose treatment outcome is unknown, and for whom "lost to follow-up" has been excluded.

2.4.7 Sustained treatment success

There is a need for assessment of treatment outcome after the end of treatment, especially of the status of the patient at certain periods after TB (e.g. if the patient is still alive, are they TB free or what is their post-TB lung health status?). Although the issue is important, there are implementation challenges in relation to post-treatment follow-up in programme settings. Some initiatives on post-TB treatment outcomes have been tested or implemented in different settings; however, it is unlikely that most countries with a high TB burden and limited resources would be able to follow up their TB cases for 6 or 12 months after the end of treatment. It was suggested that the post-treatment outcome assessment may need to be field-tested for added value, feasibility and other operational issues. The group finally suggested the definition "sustained treatment success" for post-TB treatment, which will be used for operational research only. This suggests that successfully treated TB patients be assessed at 6 months (DS-TB and DR-TB) and 12 months (DR-TB) after the end of treatment, to determine whether they are alive and TB free.

3. Consultation outcomes: the new definitions of TB treatment outcomes

Based on the discussions during the consultation, and the principles and operational issues described above, WHO proposes new definitions of TB treatment outcomes (Box 3.1). These new definitions apply to both DR-TB and DS-TB.

Box 3.1. New TB treatment outcome definitions for both DR-TB and DS-TB

Treatment failed
A patient whose treatment regimen needed to be terminated or permanently changed[a] to a new regimen or treatment strategy.

Cured
A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response[b] and no evidence of failure.

Treatment completed
A patient who completed treatment as recommended by the national policy, whose outcome does not meet the definition for cure or treatment failure.

Died
A patient who died[c] before starting treatment or during the course of treatment.

Lost to follow-up
A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

Not evaluated
A patient for whom no treatment outcome was assigned.[d]

Treatment success
The sum of cured and treatment completed.

An optional definition proposed for use in operational research only

Sustained treatment success
An individual assessed at 6 months (for DR-TB and DS-TB) and at 12 months (for DR-TB only) after successful TB treatment, who is alive and free of TB.

DR-TB: drug-resistant TB; DS-TB: drug-susceptible TB; TB: tuberculosis.

[a] Reasons for the change include:
- no clinical response and/or no bacteriological response (see note 'b');
- adverse drug reactions; or
- evidence of additional drug resistance to medicines in the regimen.

[b] "Bacteriological response" refers to bacteriological conversion with no reversion.
- "bacteriological conversion" describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are negative.
- "bacteriological reversion" describes a situation where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.

[c] Patient died for any reason.

[d] This includes cases "transferred out" to another treatment unit and those whose treatment outcome is unknown; however, it excludes those lost to follow-up.

4. Next steps

WHO will adopt the new definitions of TB treatment outcomes in 2021, and will include the updated treatment outcome definitions in new version of the WHO definitions and reporting framework for TB *(8)* and Module 4 of the operational handbook *(23)* (both documents are expected to be revised in 2021). NTPs and stakeholders will need to update their policies and orient their systems to accommodate the new definitions.

Annex 1: Historical and current definitions of treatment outcomes for patients with drug-susceptible or drug-resistant tuberculosis

Historical definitions for DR-TB		Current definitions for DS-TB and DR-TB	
Laserson et al. 2005 *(2)*	**WHO 2006 and 2008 *(4, 5)***	**WHO 2013 (DR-TB) *(8)***	**WHO 2013 (DS-TB) *(8)***
Cure An MDR-TB patient who has completed treatment according to country protocol and has been consistently culture negative (with at least five results) for the final 12 months of treatment. If only one positive culture[a] is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures, taken at least 30 days apart.	**Cured** A Category IV[b] patient who has completed treatment according to the programme's protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.	**Cured** Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[c]	**Cured** A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear or culture negative in the last month of treatment and on at least one previous occasion.
Treatment completed An MDR-TB patient who has completed treatment according to country protocol but does not meet the definition for cure or treatment failure due to lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of therapy).	**Treatment completed** A Category IV patient who has completed treatment according to the programme's protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment).	**Treatment completed** Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.	**Treatment completed** A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.

Historical definitions for DR-TB		Current definitions for DS-TB and DR-TB	
Laserson et al. 2005 *(2)*	**WHO 2006 and 2008 *(4, 5)***	**WHO 2013 (DR-TB) *(8)***	**WHO 2013 (DS-TB) *(8)***
Death An MDR-TB patient who dies for any reason during the course of MDR-TB treatment.	**Died** A Category IV patient who dies for any reason during the course of MDR-TB treatment.	**Died** A patient who dies for any reason during the course of treatment.	**Died** A TB patient who dies for any reason before starting or during the course of treatment.
Treatment default An MDR-TB patient whose MDR-TB treatment was interrupted for 2 or more consecutive months for any reason.	**Defaulted** A Category IV patient whose treatment was interrupted for 2 or more consecutive months for any reason.[d]	**Lost to follow-up** A patient whose treatment was interrupted for 2 consecutive months or more.	**Lost to follow-up** A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Treatment failure[e] Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months are positive, or if any one of the final three cultures is positive. Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early due to poor response or adverse events.	**Failed** Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. (Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events. These latter failures can be indicated separately in order to do sub-analysis.)	**Failed** Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: lack of conversion[f] by the end of the intensive phase; or bacteriological reversion[f] in the continuation phase after conversion to negative; or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or ADRs.	**Failed** A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.

Historical definitions for DR-TB		Current definitions for DS-TB and DR-TB	
Laserson et al. 2005 *(2)*	**WHO 2006 and 2008 *(4, 5)***	**WHO 2013 (DR-TB) *(8)***	**WHO 2013 (DS-TB) *(8)***
Transfer out An MDR-TB patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown.	**Transferred out** A Category IV patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown.	**Not evaluated** A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown.)	**Not evaluated** A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
		Treatment success The sum of cured and treatment completed.	**Treatment success** The sum of cured and treatment completed.

ADR: adverse drug reaction; DR-TB: drug-resistant TB; DS-TB: drug-susceptible TB; MDR-TB: multidrug-resistant TB; TB: tuberculosis; WHO: World Health Organization.

[a] A positive culture requires >10 colonies on solid media; two consecutive positive cultures must be obtained if <10 colonies are detected in the first culture; if the second culture also contains <10 colonies, the culture should be interpreted as positive *(2)*.

[b] At the time, diagnostic category IV patients included patients with confirmed MDR-TB, suspected MDR-TB or poly-resistant TB *(5)*.

[c] For treatment failed, lack of conversion by the end of the intensive phase implies that the patient did not convert within the maximum duration of the intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between the intensive and continuation phases, a cut-off of 8 months after the start of treatment is suggested, to determine when the criteria for "cured", "treatment completed" and "treatment failed" apply.

[d] In 2008, the words "without medical approval" were added to the end of this sentence *(5)*.

[e] This was a programmatic definition for cohort analysis; thus, after a patient fails, countries were encouraged to perform susceptibility testing for second-line drugs to find a treatment option for the patient or continue treatment after a programmatic outcome had been assigned *(2)*.

[f] The terms "conversion" and "reversion" of culture as used here are defined as follows: **conversion (to negative):** culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion; **reversion (to positive):** culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are positive. For the purpose of defining "treatment failed", reversion is considered only when it occurs in the continuation phase *(8)*.

Annex 2: Proposed revisions to treatment outcome definitions from the scientific literature

First author and year of publication			
Schwoebel 2019 *(9)*	**Gunther 2016** *(10)*	**Dedicoat 2017** *(24)*	**Migliori 2019** *(13)*
Cure Treatment completed without evidence of failure AND two consecutive negative cultures[a] taken ≥30 days apart, one of them after 6 months of treatment.	**Cure** A negative culture status 6 months after treatment initiation, no positive culture thereafter, and no relapses within 1 year after treatment completion.	**Cure** Should preferably include a period of being free of recurrent disease (e.g. 12 months after completion of TB treatment, when most relapses are expected to have occurred).	**Cured** For programmatic and international comparison purposes, the present WHO definition remains valid. However, recurrences after treatment completion would need to differentiate between relapse (disease caused by the same strain) and reinfection (disease caused by a different strain). Where possible, acquired drug resistance during and after treatment should be identified separately, because this provides important information on system vulnerability.
Treatment completed Patient who has completed treatment without evidence of failure BUT who does not meet the criteria for cure.	*Not mentioned*	*Not mentioned*	*Not mentioned*
Died Patient who died for any reason during the course of treatment.	**Death** Death during observation.	*Not mentioned*	**Died** As above (i.e. for cured).
Lost to follow-up Patient whose treatment was interrupted for ≥ 2 consecutive months.	**Lost to follow-up** Non-receipt of care 6 months after treatment initiation.	*Not mentioned*	*Not mentioned*

First author and year of publication			
Schwoebel 2019 *(9)*	**Gunther 2016** *(10)*	**Dedicoat 2017** *(24)*	**Migliori 2019** *(13)*
Treatment failure Treatment termination or need for permanent regimen change of two or more drugs due to: • one or more positive cultures after ≥6 months of treatment, except for isolated positive culture (i.e. a positive culture preceded by at least one and followed by two or more negative cultures); or • two or more consecutive grade ≥ 2+ sputum smears after 6 months of treatment (if cultures are not available).[b]	**Failure** A positive culture status 6 months after treatment initiation or thereafter or a relapse within 1 year after treatment completion.	**Failure** Reclassifying recurrence of disease during 12 months after treatment as failure (in the absence of other biomarkers).	**Treatment failure** This definition needs to be revisited. Evidence of acquired resistance to fluoroquinolones or injectables, or ADRs to these drugs, does not necessarily imply treatment failure, especially in view of the use of the new recommended regimen based on Group A drugs.
Not evaluated Patient for whom no treatment outcome is assigned (includes cases who are transferred out to another treatment unit and whose treatment outcome is not known).	**Undeclared outcome** An outcome that was not assessed (owing to transferral out of the cohort, no culture status at 6 months while the patient was receiving care, or no post-treatment assessment).	*Not mentioned*	*Not mentioned*
Treatment success Sum of "cured" and "treatment completed".	*Not mentioned*	*Not mentioned*	*Not mentioned*

ADR: adverse drug reaction; AFB: acid-fast bacilli; TB: tuberculosis; WHO: World Health Organization.

[a] A minimum of three cultures should be performed: one before treatment initiation (M0), one at the end of intensive phase (M4, M5 or M6 if the intensive phase is prolonged) and one after 6 months of treatment. Additional specimens should be requested in case of one positive culture after 6 months to either confirm failure or prove that a positive culture is isolated.

[b] Smears should be performed on sputum specimen taken before initiation of treatment (M0), and then monthly (M: M1, M2, M3, M4, M5, M6, M7, M8, M9, and possibly M10 and M11 if the intensive phase is prolonged). Smears should be performed on two specimens at M4, and again at M5 if positive at M4, to allow the physician to decide whether the intensive phase should be prolonged. Results are classified as follows: rare = 1–9 AFB/100 fields; 1+ = 10–99 AFB/100 fields; 2+ = 1–9 AFB/field; and 3+ = ≥10 AFB/field.

Annex 3: Treatment outcome definitions for patients with rifampicin resistant, multidrug-resistant and extensively drug-resistant tuberculosis treated using novel second-line treatment regimens as part of clinical trials

Name of trial and definition of treatment outcomes relevant to the treatment of DR-TBs				
STREAM[a] trial Stage 2	**EndTB trial[b]**	**BPaL[c]**	**TB-PRACTECAL[d]**	**Union Short MDR-TB Regimen observational study[e]**
Primary efficacy outcome: the proportion of patients with a favourable outcome at week 76.	Proportion of participants with a favourable outcome at week 73. A participant's outcome will be classified as favourable at week 73 if the outcome is not classified as unfavourable, and one of the following is true: • the last two culture results are negative. These two cultures must be taken from sputum samples collected on separate visits, the latest between weeks 65 and 73; • the last culture result (from a sputum sample collected between weeks 65 and 73) is negative; and either there is no other post-baseline culture result, or the penultimate culture result is positive due to laboratory cross contamination; and bacteriological, radiological and clinical evolution is favourable; or	Primary outcome measures: incidence of bacteriological failure or relapse or clinical failure through follow-up until 6 months after the end of treatment. Bacteriological failure: during the treatment period, failure to attain culture conversion to negative. Bacteriological relapse: during the follow-up period, failure to maintain culture conversion to negative status in culture, with culture conversion to positive status with a *Mycobacterium tuberculosis* strain that is genetically identical to the infecting strain at baseline. Clinical failure: a change from protocol-specified TB treatment due to treatment failure, retreatment for TB during follow-up, or TB-related death.	Primary outcome measures: Stage 1: Percentage of patients with culture conversion in liquid media at 8 weeks post-randomization [time frame: 8 weeks post-randomization]. Stage 1: Percentage of patients who discontinue treatment for any reason or die [time frame: 8 weeks post-randomization]. Stage 2: Percentage of patients with an unfavourable outcome (failure, death, recurrence, lost to follow-up) [time frame: 72 weeks post-randomization].	Cured: treatment completed as per the national policy without proof of failure AND three or more consecutive cultures taken ≥ 30 days apart are negative. Treatment completed: treatment completed as per the national policy without evidence of failure BUT no record that three or more consecutive cultures taken ≥ 30 days apart are negative. Treatment failed: positive culture after ≥ 6 months of treatment, except for isolated positive cultures (i.e. positive culture preceded by at least one and followed by two or more negative cultures).

Name of trial and definition of treatment outcomes relevant to the treatment of DR-TBs				
STREAM[a] trial Stage 2	**EndTB trial[b]**	**BPaL[c]**	**TB-PRACTECAL[d]**	**Union Short MDR-TB Regimen observational study[e]**
	• there is no culture result from a sputum sample collected between weeks 65 and 73 or the result of that culture is positive because of laboratory cross contamination; the most recent culture result is negative; and bacteriological, radiological and clinical evolution is favourable.	Note: culture conversion requires at least two consecutive culture negative/positive samples at least 7 days apart. Patients who are documented at a visit as unable to produce sputum and who are clinically considered to be responding well to treatment will be considered culture negative at that visit.		

DR-TB: drug-resistant TB; MDR-TB: multidrug-resistant TB; TB: tuberculosis.

[a] STREAM is the trial: Evaluation of a Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis. The regimens being used are (1) a 9-month regimen of 4 months of bedaquiline, levofloxacin, high-dose isoniazid, prothionamide, clofazimine, ethambutol and pyrazinamide, followed by 5 months of bedaquiline, levofloxacin, clofazimine, ethambutol and pyrazinamide; and (2) a 6-month regimen of bedaquiline, levofloxacin, clofazimine, pyrazinamide, high-dose isoniazid and kanamycin, with isoniazid and kanamycin only given for the first 2 months. The duration of treatment is 6–9 months, depending on the regimen being used. Information on the STREAM Stage 2 trial is available at https://clinicaltrials.gov/ct2/show/NCT02409290.

[b] The EndTB trial is testing five intervention regimens compared with standard care. The duration of the regimens is 9 months. The composition of the regimens is available at https://clinicaltrials.gov/ct2/show/NCT02754765. A separate clinical trial (called the endTB-Q trial) is being implemented to treat patients with MDR-TB and additional fluoroquinolone resistance.

[c] The BPaL study was also called the Nix-TB study. BPaL is an acronym for the three medicines used in the regimen; namely, bedaquiline, pretomanid and linezolid. The duration of treatment is 6 months, extendable to 9 months. Information on the BPaL regimen/ the NixTB study is available at https://clinicaltrials.gov/ct2/show/NCT02333799 and in Conradie et al. 2020 (25).

[d] TB-PRACTECAL is the trial: Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s). It is evaluating three treatment regimens containing bedaquiline and pretomanid in combination with existing and repurposed anti-TB drugs, compared with standard care. Culture conversion is defined as at least two consecutive negative sputum cultures taken 4 weeks apart (±2 weeks). The duration of the regimens is 6 months. Information on the TB-PRACTECAL study is available at https://clinicaltrials.gov/ct2/show/NCT02589782.

[e] The Union Short MDR-TB Regimen observational study was a regimen of moxifloxacin, clofazimine, ethambutol, pyrazinamide, kanamycin, prothionamide and high-dose isoniazid, given for a duration of 9 months, extendable to 11 months *(9)*.

Annex 4: Agenda for the consultation meeting on the drug-resistant tuberculosis treatment outcome definitions

Tuesday 17 November 2020		
Time (CET)	**Topic**	**Speaker or chair**
14.00–14.15	Welcome and opening statements	Tereza Kasaeva Director Global TB Programme, WHO
14.15–14.35	Brief introduction and meeting objectives	Fuad Mirzayev
14.35–14.55	Future of treatment monitoring and correlates of cure	Morten Ruhwald
14.55–15.15	Summary of participants' feedback on the concept note and options for revision of the treatment outcome definitions	Medea Gegia
15.15–15.35	Short break with free discussion	
15.35–17.00	Moderated discussion on the principles underlying a change in the DR-TB treatment outcome definitions: Challenges for updating the treatment outcome definitions	Session chair: Cathy Hewison Linh Nguyen
Wednesday 18 November 2020		
14.00–15.20	Discussion on the DR-TB treatment outcome definitions: "Failed"	Session chair: Cathy Hewison
15.20–15.40	Short break with free discussion	
15.40–17.00	Discussion on the DR-TB treatment outcome definitions: "Cured"	
Thursday 19 November 2020		
14.00–14.15	Brief recap of where we are at	Matteo Zignol
14.15–15.20	Discussion on the DR-TB treatment outcome definitions: "Completed", "Lost to follow-up", "Not evaluated"	Session chair: Charles Daley
15.20–15.40	Short break with free discussion	
15.40–16.45	Discussion on the DR-TB treatment outcome definitions: Outcomes beyond end of treatment, and other issues	Session chair: Charles Daley
16.45–17.00	Summary and next steps	Matteo Zignol

Annex 5: List of participants for the consultation meeting on the drug-resistant tuberculosis treatment outcome definitions

No.	Name	Organization	Country
1	Charles Daley	National Jewish Health	United States of America
2	Carole Mitnick	Partners in Health	United States of America
3	Christoph Lange	Research Center Borstel	Germany
4	GB Migliori	Maugeri Care and Research Institute, Tradate	Italy
5	Mario Raviglione	University of Milan	Italy
6	Jonathon Campbell	McGill University	Canada
7	Hoang Thanh Thuy	National tuberculosis programme (NTP)	Viet Nam
8	Maria Rodriguez	NTP	Dominican Republic
9	Welile Sikhondze	NTP	Eswatini
10	Norbert Ndjeka	NTP	South Africa
11	Anastasia Samoilova	NTP/Ministry of Health	Russian Federation
12	Yuhong Liu	China Centers for Disease Control and Prevention (CDC)	China
13	Kuldeep Sachdeva	NTP	India
14	Daniele Maria Pelissari	NTP	Brazil
15	Andrei Mosneaga	Stop TB Partnership	Switzerland
16	Sreenivas Nair	Stop TB Partnership	Switzerland
17	Morten Ruhwald	Foundation for Innovative New Diagnostics (FIND)	Switzerland
18	Cathy Hewison	Médecins sans Frontières	France
19	Fraser Wares	KNCV	The Netherlands
20	Grania Brigden	The Union	France
21	Draurio Barreira	Unitaid	Switzerland
22	Mohammed Yassin	Global Fund to Fight AIDS, Tuberculosis and Malaria	Switzerland
23	Marlena Kaczmarek	European Centre for Disease Prevention and Control	Sweden
24	Mukadi Ya Diul	United States Agency for International Development	United States of America
25	Dumitru Chesov	State University of Medicine and Pharmacy	Republic of Moldova

No.	Name	Organization	Country
26	Chen Yuan Chiang	The Union	France
27	James Seddon	Imperial College London	United Kingdom of Great Britain and Northern Ireland
28	Tony Garcia-Prats	The University of Stellenbosch	South Africa
29	Daniela Cirillo	Supranational reference laboratory (SRL) Milan	Italy
30	Harald Hoffman	SRL Gauting	Germany
31	Sarabjit Chadha	Global Drug-resistant TB Initiative	India
32	Dissou Affolabi	SRL Cotonou	Benin
33	Thandar Hmun	NTP	Myanmar
34	Renzong Li	China CDC	China
35	Sabira Tahseen	National reference laboratory (NRL)	Pakistan
36	Amir Khan	Civil Society Taskforce	Pakistan
37	Choub Sok Chamreun	KHANA (Khmer HIV/AIDS NGO Alliance)	Cambodia
38	Nino Lomtadze	NTP	Georgia
39	Mon Basilio	NRL	Philippines
40	Dan Everitt	TB Alliance	United States of America
41	Xia Hui	NRL/China CDC	China

No.	Name	World Health Organization (WHO) staff	Country
42	Tauhid Islam	WHO Regional Office for the Western Pacific (WPRO)	Philippines
43	Mukta Sharma	WHO Regional Office for South-East Asia (SEARO)	India
44	Vineet Bhatia	WHO SEARO	India
45	Askar Yedilbayev	WHO Regional Office for Europe (EURO)	Denmark
46	Rafael Lopez Olarte	WHO Regional Office for the Americas (PAHO)	United States of America
47	Kenza Bennani	WHO Regional Office for the Eastern Mediterranean (EMRO)	Egypt
48	Michel Gasana	WHO Regional Office for Africa (AFRO)	Congo
49	Jean Louis Abena	WHO AFRO	Congo
50	Kyung Oh	WHO WPRO	Philippines
51	Tereza Kasaeva	WHO Global TB Programme	Switzerland
52	Matteo Zignol	WHO Global TB Programme	Switzerland
53	Fuad Mirzayev	WHO Global TB Programme	Switzerland
54	Medea Gegia	WHO Global TB Programme	Switzerland
55	Linh Nguyen	WHO Global TB Programme	Switzerland
56	Kerri Viney	WHO Global TB Programme	Switzerland
57	Dennis Falzon	WHO Global TB Programme	Switzerland
58	Ernesto Jaramillo	WHO Global TB Programme	Switzerland
59	Nazir Ismail	WHO Global TB Programme	Switzerland
60	Philippe Glaziou	WHO Global TB Programme	Switzerland
61	Anna Dean	WHO Global TB Programme	Switzerland
62	Hazim Timimi	WHO Global TB Programme	Switzerland
63	Marek Lalli	WHO Global TB Programme	Switzerland
64	Marie-Christine Bartens	WHO Global TB Programme	Switzerland
65	Charalampos Sismannidis	WHO Global TB Programme	Switzerland
66	Olga Tosas-Auguet	WHO Global TB Programme	Switzerland

Annex 6: Options proposed for discussion at the consultation meeting on the update of treatment outcome definitions for patients treated for drug resistant and drug susceptible tuberculosis

Out-comes	Alternative options and definitions			Current definitions (DR-TB)	Current definitions (DS-TB)
	Option 1 (DR-TB only)	Option 2 (DR-TB only)	Option 3 (for both DR-TB and DS-TB)		
Treatment failed	A patient whose treatment needed to be terminated or permanently changed to a new regimen.[a]	A patient whose treatment needed to be terminated or permanently changed to a new regimen.[b]	A patient whose treatment needed to be terminated or permanently changed to a new regimen.[b]	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: – lack of conversion by the end of the intensive phase; or – bacteriological reversion in the continuation phase after conversion to negative; or – evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs; or – ADRs.	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.

Out-comes	Alternative options and definitions			Current definitions (DR-TB)	Current definitions (DS-TB)
	Option 1 (DR-TB only)	Option 2 (DR-TB only)	Option 3 (for both DR-TB and DS-TB)		
Cured	A pulmonary TB patient with bacteriologically confirmed[c] DR-TB at the beginning of treatment who completed treatment as recommended by the national policy and was sputum smear or culture negative in the last month of treatment and on at least one previous occasion.	A pulmonary TB patient with bacteriologically confirmed DR-TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological conversion and no evidence of failure.	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological conversion and no evidence of failure.	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear or culture negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A patient who completed treatment as recommended by the national policy without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.	A patient who completed treatment as recommended by the national policy and whose outcome does not meet the definition for cure or failure.	A patient who completed treatment as recommended by the national policy and whose outcome does not meet the definition for cure or failure.	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.

Out-comes	Alternative options and definitions			Current definitions (DR-TB)	Current definitions (DS-TB)
	Option 1 (DR-TB only)	Option 2 (DR-TB only)	Option 3 (for both DR-TB and DS-TB)		
Died	A patient who died[d] before starting or during the course of treatment.	A patient who died[d] before starting or during the course of treatment.	A patient who died[d] before starting or during the course of treatment.	A patient who dies for any reason during the course of treatment.	A TB patient who dies for any reason before starting or during the course of treatment.
Lost to follow-up	A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.	A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.	A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.	A patient whose treatment was interrupted for 2 consecutive months or more.	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome was assigned.[e]	A patient for whom no treatment outcome was assigned.[e]	A patient for whom no treatment outcome was assigned.[e]	A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown.)	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of cured and treatment completed.	The sum of cured and treatment completed.	The sum of cured and treatment completed.	The sum of cured and treatment completed.	The sum of cured and treatment completed.

ADR: adverse drug reaction; DR-TB: drug-resistant TB; DS-TB: drug-susceptible TB; TB: tuberculosis.

[a] Examples of reasons for assigning the outcome "treatment failure" include sputum smear or culture positive in the last month of treatment and on at least one previous occasion;[i] evidence of additional acquired resistance to at least one of the medicines in the treatment regimen; or ADRs.

[b] Examples of reasons for assigning the outcome "treatment failure" include lack of conversion;[ii] reversion;[iii] evidence of additional acquired resistance to medicines in the regimen; or ADRs.

[c] A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture or WHO-recommended rapid diagnostic test (e.g. Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started.

[d] Patient died for any reason.

[e] This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown.

[i] *This may be problematic for longer regimens because the treatment outcome cannot be assigned until the end of treatment and clinicians may want to take action before this.*

[ii] *Bacteriological conversion: at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken at least 30* days *apart, are negative.*

[iii] *Bacteriological reversion: at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken at least 30* days *apart, are positive.*

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