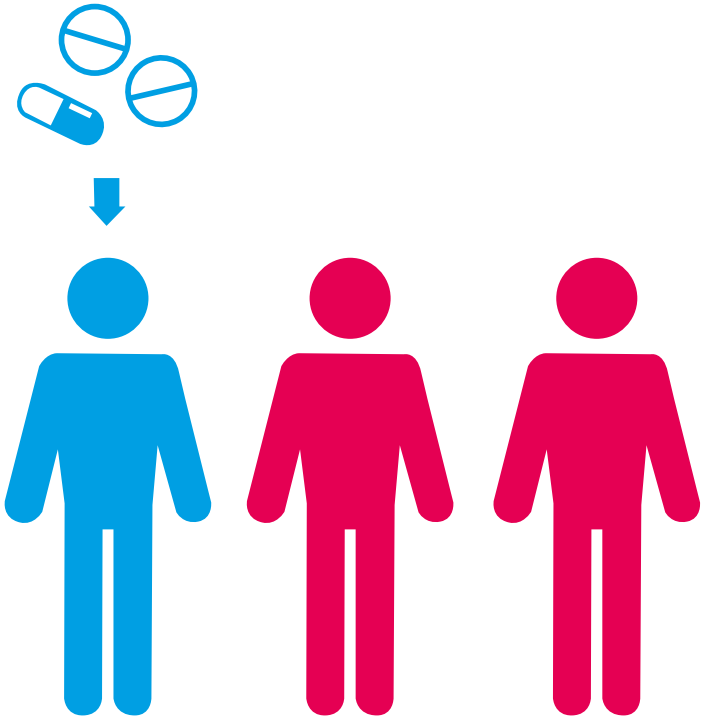
Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis,

27-29 October 2020



World Health Organization

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Abbreviations and acronyms

AIDS	acquired immunodeficiency syndrome
BPaL	bedaquiline, pretomanid and linezolid
CDC	Centers for Disease Control and Prevention (United States)
CI	confidence interval
DR-TB	drug-resistant tuberculosis
DST	drug-susceptibility testing
gDST	genotypic drug-susceptibility testing
GLC	Green Light Committee
HIV	human immunodeficiency virus
LPA	line probe assay
M. tuberculosis	*Mycobacterium tuberculosis*
MDR/RR-TB	multidrug-resistant or rifampicin-resistant tuberculosis
MDR-TB	multidrug-resistant tuberculosis
MIC	minimum inhibitory concentration
NGS	next-generation sequencing
NTP	national tuberculosis programme
OR	odds ratio
pDST	phenotypic drug-susceptibility testing
RR-TB	rifampicin-resistant tuberculosis
SL	second line
SLD	second-line drug
TB	tuberculosis
US	United States
USA	United States of America
WHO	World Health Organization
XDR	extensively drug resistant

Executive summary

The World Health Organization (WHO) consultation meeting on the definition of extensively drug-resistant (XDR) tuberculosis (TB) was held on 27–29 October 2020 as an online meeting, organized by the Global TB Programme, WHO, Geneva, Switzerland. Some 73 participants attended the meeting, representing countries, bilateral and multilateral agencies, international organizations, nongovernmental organizations, civil society and academia.

The overall goal of the meeting was to determine how recent changes in treatment regimens and diagnostics for drug-resistant TB (DR-TB) impact on the definition of XDR-TB, with a view to exploring its revision. The currently used definition of XDR-TB was formulated in 2006 at a meeting of the Global Taskforce on XDR-TB, convened by WHO, and has been in use for clinical and surveillance purposes since that time.

The specific meeting objectives were to:

- discuss recent changes in treatment regimens and diagnostics for DR-TB, and to determine how these affect the definition of XDR-TB;
- discuss options for changing the definition of XDR-TB, including the pros and cons of these options, with various perspectives in mind (e.g. clinical, programmatic and surveillance perspectives);
- discuss some overarching principles that need to be borne in mind when thinking about a new definition of XDR-TB; and
- discuss a proposal for a new definition of XDR-TB that has global application, and that can be used for surveillance, programmatic and clinical purposes.

Owing to global travel restrictions and other directives imposed in response to the COVID-19 pandemic, the meeting was structured as three online meetings of 3 hours each, held over 3 consecutive days. The majority of the meeting was devoted to discussion, structured around four sessions:

- epidemiological trends, new evidence and updated guidelines;
- operational, implementation and strategic issues related to the definition of XDR-TB;
- principles that will underlie the new definition of XDR-TB; and
- an outline of the new definition of XDR-TB, including next steps.

A detailed concept note was prepared by the WHO Global TB Programme and shared with participants in advance of the meeting. This note provided an historical overview of the definition of XDR-TB, updates on WHO recommendations on TB treatment and diagnostics, an overview of the epidemiology of multidrug-resistant TB (MDR-TB) and XDR-TB (as currently defined), a rationale for a potential change in the definition of XDR-TB and some proposed options. The concept note highlighted the following:

- The current definition of XDR-TB has retained some value because resistance to fluroquinolones is linked to a reduction in favourable treatment outcomes, and leads to one of the following:

  – an important choice between the shorter and longer WHO-recommended regimens (including the one currently recommended under operational research conditions); or
  – a significant modification in the design of the longer regimen.

- Injectable agents have lost their priority ranking over the past decade, having been replaced by other, more effective oral agents for the treatment of MDR-TB that could cause fewer adverse events and less inconvenience. Thus, WHO now recommends against the use of kanamycin and capreomycin, and there has been a significant deprioritization of amikacin (and of streptomycin).

- Resistance to two important priority medicines, bedaquiline and linezolid, is currently rare; however, it is being reported and is more consequential to contemporary and future regimens than resistance to injectable agents. This resistance is not reflected in the current XDR-TB definition.

Meeting participants reviewed current data on the epidemiology of MDR-TB and XDR-TB, current WHO recommendations on TB diagnostics and treatment, and the results of a study that used an individual patient dataset to assess whether the existing definitions of MDR-TB and XDR-TB, and the informal pre-XDR-TB definition, remain adequate to identify different levels of disease severity or clinical management, in view of the recent changes in WHO recommendations.

Participants suggested that a revised definition of XDR-TB was necessary to keep pace with changes in policy and practice. In particular, they noted the lowered priority of the injectable agents and the importance of bedaquiline, the fluoroquinolones and linezolid (e.g. Group A drugs). Among the strategic and operational issues noted were the use of regimens that contain Group A drugs; current and future availability of drug-susceptibility testing (DST); the role of the XDR-TB definition in advocacy and communication; the potential stigma associated with definitions; clinical decision-making (which is partly informed by DST); surveillance; and other programmatic considerations.

The overarching principles that participants set to guide the development of a revised definition of XDR-TB were that the definition should be:

- simple;
- measurable;
- relevant to programmes, including for surveillance and clinical management; and
- future-proof (i.e. able to be used for a certain period of time despite expected changes in practice).

Pre-XDR-TB: TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone[a]

XDR-TB: TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone[a] and at least one additional Group A drug[b]

[a] The fluoroquinolones include levofloxacin and moxifloxacin, because these are the fluoroquinolones currently recommended by WHO for inclusion in shorter and longer regimens.
[b] The Group A drugs are currently levofloxacin or moxifloxacin, bedaquiline and linezolid; therefore, XDR-TB is MDR/RR-TB that is resistant to a fluoroquinolone and either bedaquiline or linezolid (or both). The Group A drugs may change in the future; therefore, the terminology "Group A" is appropriate here and will apply to any Group A drugs in the future.

Bearing these principles in mind, and recognizing the current strategic and operational issues (as described by meeting participants), the WHO proposes a definition of pre-XDR-TB as well as a revised definition of XDR-TB. The definition of MDR-TB will remain the same for the time being. The agreed definitions are as follows:

MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; TB: tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

These definitions should be applied from January 2021. They will define the group of TB patients who will require a significantly different treatment approach in order to attain better treatment outcomes, without major delays in accessing the treatment. The definitions will also need to be adopted for use in surveillance and epidemiological reporting, to flag both the seriousness of the situation and as a measure of progress against national and global epidemiological indicators to end TB as a public health problem.

1. Background and current evidence

1.1 Background and history

Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to at least isoniazid and rifampicin; it emerged as a threat to tuberculosis (TB) control worldwide in the 1990s. This form of TB required the use of second-line drugs (SLDs) that were less effective, more toxic and costlier than the first-line isoniazid- and rifampicin-based regimens. MDR-TB was the first infectious condition to alert national authorities worldwide to the importance of antimicrobial resistance as a public health challenge of the future (1).

In 2000, the World Health Organization (WHO), together with several technical partners, established the Green Light Committee (GLC) (2). The GLC strived to increase access to SLDs worldwide and to ensure the proper use of SLDs, to prevent additional and increased drug resistance. While advising MDR-TB treatment programmes worldwide, the GLC witnessed reports of multiple cases of MDR-TB that had additional resistance to many SLDs. To assess the frequency and distribution of these cases, the United States (US) Centers for Disease Control and Prevention (CDC) and WHO surveyed the laboratories that were then part of the TB Supranational Reference Laboratory Network (3). The survey concluded in March 2006 (4) with a worrying result – it showed that about 2% of all MDR-TB strains (estimated to represent about 20 000 cases worldwide) available in these laboratories were exhibiting resistance to other SLDs, in addition to resistance to rifampicin and isoniazid. A complementary study of population-based data on the drug-susceptibility patterns of TB isolates from three countries showed even higher proportions of additional resistance in MDR-TB patients: Latvia (19%), the Republic of Korea (15%) and the United States of America (USA, 4%) (4). The working definition in these studies defined extensively drug-resistant TB (XDR-TB) (5) as TB isolates resistant to isoniazid and rifampicin, and at least three of the six main classes of SLDs (e.g. aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine and *p*-aminosalicylic acid). At a time when treatment options for MDR-TB were meagre and the evidence for the best treatment approaches was limited, XDR-TB was considered a formidable threat to public health and TB control. This raised concerns of a future epidemic of virtually untreatable TB, with severely restricted treatment options that would not be effective for patients and that could jeopardize the gains made in global TB control.

Recognizing the global importance of the emerging problem of drug-resistant TB (DR-TB), WHO released its first guidelines on the management of DR-TB in 1996 (updated in 1997) (6). These guidelines were extensively updated in 2006, with new content on how to include a DR-TB component within programmatic TB services (7). The management of XDR-TB was included in a revised edition in 2008 (8)Emergency update 2008 (WHO/HTM/TB/2008.402.

In 2006, an outbreak of XDR-TB in people coinfected with HIV around a rural hospital in Tugela Ferry (KwaZulu-Natal Province, South Africa) (9) received widespread international attention. The outbreak highlighted the high case-fatality associated with XDR-TB in this setting, and the possibility of transmission of drug-resistant forms of TB among people with weakened immunity in the absence of effective treatment. In June 2006, WHO's Strategic and Technical Advisory Group for TB urged WHO to take immediate and effective action to address MDR-TB and XDR-TB in the WHO African Region.

In September 2006, an expert consultation meeting was jointly organized by the South African Medical Research Council, WHO and the US CDC, in Johannesburg, South Africa ***(10)***. International concerns related to the emergence of XDR-TB were also heightened by reports from KwaZulu-Natal Province of high mortality rates in people coinfected with HIV and XDR-TB, beyond the initial Tugela Ferry outbreak. The outcome of this meeting was the development of a series of

steps designed to limit the impact of MDR-TB and XDR-TB globally. These steps were incorporated into a seven-point plan of action, which included both short-term and long-term actions to be implemented by countries and partners.[1]

In October 2006, the WHO TB and HIV departments organized a meeting of the WHO Global Task Force on XDR-TB at WHO headquarters in Geneva, Switzerland, in response to the XDR-TB emergency and as a follow-up to the expert consultation (11). More than 110 participants representing the most affected countries attended the meeting, together with global experts in TB control and MDR-TB management; HIV prevention, care and control; infection control and occupational health; diagnostics; communicable disease preparedness and response; and advocacy, communication and social mobilization; as well as representatives from bilateral and multilateral agencies and organizations. The task force discussed the need for a revised definition of XDR-TB and concluded with a definition, which has been in use since this time for both surveillance and clinical purposes (Box 1). Another WHO expert consultation held in 2012, in the wake of reports from India and elsewhere of XDR-TB with additional drug resistance, proposed no changes to the XDR-TB definition but supported continued vigilance for the emergence of such strains (12). A new definition of resistance beyond XDR-TB ("total DR-TB") was not considered feasible, given technical difficulties with drug-susceptibility testing (DST) for many anti-TB medicines, the lack of standardized DST methods for several anti-TB drugs (including new investigational drugs) and insufficient evidence to link such DST results to treatment outcomes. At the time of the 2012 meeting, DST for drugs used to define XDR-TB (i.e. the injectable drugs and the fluoroquinolones) were the only ones considered accurate and reproducible. The meeting considered that there was a critical need for properly conducted studies, in different epidemiological settings, linking DST results to treatment outcomes.

Box 1. Pre-2021 definition of XDR-TB, formulated in 2006 (13)

XDR-TB: TB that is resistant to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance

TB: tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

1.2 Global epidemiology of MDR/RR-TB and XDR-TB

1.2.1 Epidemiology and detection of XDR-TB