New definitions of pre-extensively and extensively drug-resistant tuberculosis: update from the World Health Organization

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The definition of extensively drug resistant tuberculosis has been updated by the World Health Organization and pre-extensively drug-resistant tuberculosis has been defined https://bit.ly/30Fdffc

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Background

Multidrug-resistant tuberculosis (MDR-TB), defined as *Mycobacterium tuberculosis* with resistance to at least isoniazid and rifampicin [1], emerged as a threat to tuberculosis (TB) control worldwide in the 1990s [2]. This form of TB required the use of second-line drugs that were less effective, more toxic and costlier than first-line isoniazid- and rifampicin-based regimens. MDR-TB was one of the first infectious conditions to alert national authorities worldwide to the importance of antimicrobial resistance as a public health challenge of the future, further emphasised by outbreaks of MDR-TB in the USA and Europe [3–5]. Recognising the global importance of this emerging problem, the World Health Organization (WHO) released its first guidelines on the management of drug-resistant TB in 1996 and has updated them regularly since [1, 6].

In 2004–2005, concerns about the existence of MDR-TB with additional drug resistance prompted the US Centers for Disease Control and Prevention (CDC) and WHO to carry out a survey of laboratories that were then part of the TB Supranational Reference Laboratory Network [7]. The survey concluded in March 2006 [8] with a worrying result that about 2% of all MDR-TB strains (estimated to represent about 20 000 cases worldwide) were exhibiting resistance to second-line drugs, in addition to resistance to rifampicin and isoniazid [8]. 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 USA (4%) [8]. For the first time, these studies defined extensively drug-resistant TB (XDR-TB) as TB caused by *M. tuberculosis* strains resistant to isoniazid and rifampicin, and at least three of the six main classes of second-line drugs (*e.g.* aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine and p-aminosalicylic acid) [8, 9].

In 2006, an outbreak of XDR-TB in people coinfected with HIV around a rural hospital in Tugela Ferry (KwaZulu-Natal Province, South Africa) [10] received widespread international attention [11]. The

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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 [10].

In response, an expert consultation meeting was jointly organised by the South African Medical Research Council, WHO and the US CDC in September 2006 [12]. The outcome of this meeting was the development of a series of steps and a plan of action designed to limit the impact of MDR-TB and XDR-TB globally [13]. Then, in October 2006, the WHO organised a meeting of the Global Task Force on XDR-TB in response to the XDR-TB emergency and as a follow-up to the expert consultation [14]. The task force concluded with a revised XDR-TB definition, which has been in use since that time for both surveillance and clinical purposes (table 1) [13]. In addition, a related definition of pre-XDR-TB, characterised as MDR-TB plus resistance to a fluoroquinolone or a second line injectable agent, has been in use in the scientific literature [15].

The need to revise the definition of XDR-TB

New tests to diagnose MDR- or rifampicin-resistant TB (RR-TB), as well as the medicines and regimens used to treat it, have been developed during the last decade [16, 17]. In 2018, WHO recommended to remove two injectable agents, kanamycin and capreomycin, from the list of medicines for the treatment of MDR/RR-TB [18]. The injectable agent amikacin was deprioritised for use in longer regimens but remained as part of the standardised shorter regimen [18]. In 2020, WHO moved to recommend an all-oral shorter regimen to treat MDR/RR-TB, resulting in a phasing out of the use of injectable drugs in both the longer and shorter regimens [1]. In particular, injectable agents are no longer recommended as part of the shorter regimen, which is now an all-oral bedaquiline-containing regimen and has largely been standardised [1]. In the priority classification of second-line drugs recommended when designing individualised longer regimens, injectable agents (amikacin and streptomycin) have been deprioritised to group C [1].

Given these developments, it had become clear that the 2006 definition of XDR-TB, which was based on resistance to fluoroquinolones and the second line injectable agents in addition to MDR-TB, has only partially retained its value and relevance [19]. Resistance to fluoroquinolones is linked to a reduction in favourable treatment outcomes [20], and leads to an important choice between the shorter and longer WHO-recommended regimens, or a significant modification in the design of the longer regimen. The second-line 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/RR-TB that could cause fewer adverse events and less inconvenience [21–23].

In addition, resistance to two important priority medicines, namely bedaquiline and linezolid, is currently rare as these drugs have only recently been introduced to treat TB; however, resistance is being reported from multiple countries [24, 25]. This resistance is not reflected in the existing XDR-TB definition.

WHO-convened consultation to review the definition of XDR-TB

In October 2020, the WHO Global TB Programme convened an online expert consultation meeting on the definition of XDR-TB [26]. Approximately 70 participants attended the meeting, representing clinicians, researchers, laboratory specialists, public health specialists and community representatives from member states, bilateral and multilateral agencies, international organisations, nongovernmental organisations, civil society and academia.

The meeting objectives were to determine how recent changes in treatment regimens and diagnostics for drug-resistant TB affect the definition of XDR-TB and discuss a proposal for a new definition that has global application, and that can be used for surveillance, programmatic and clinical purposes [26].

Materials shared with and presented to the meeting participants included a detailed concept note, current data on the epidemiology of MDR/RR-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/RR-TB and XDR-TB, and the informal pre-XDR-TB definition,

TABLE 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 TB.

remain adequate to identify different levels of disease severity or clinical management, in view of the recent changes in WHO recommendations [26].

Participants noted the lowered priority of the second-line injectable agents and the importance of the fluoroquinolones (*e.g.* levofloxacin and moxifloxacin), bedaquiline and linezolid (*e.g.* group A drugs), and their implications in designing MDR-TB treatment regimens. The utility of having a formal definition of pre-XDR-TB was also discussed during the consultation. Several strategic and operational issues that were important when thinking about a revised definition of XDR-TB were considered [27]. Among these issues 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 for patients detected with XDR-TB; clinical decision-making (which is informed by DST); surveillance; and other programmatic considerations.

Meeting participants discussed some overarching principles that could guide the development of a revised definition of XDR-TB, making it: simple, measurable, relevant to national TB 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 drug use and regimen composition) [26].

Based on the discussions, bearing the principles in mind, and recognising the current strategic and operational issues, the meeting concluded with WHO proposing a definition of pre-XDR-TB as well as a revised definition of XDR-TB. The definition of MDR-TB will remain the same and is: TB caused by *M. tuberculosis* strains that are resistant to at least both rifampicin and isoniazid [16]. As well, the definition of rifampicin resistance remains as: TB caused by *M. tuberculosis* strains resistant to rifampicin [16]. These strains may be susceptible or resistant to isoniazid (*i.e.* MDR-TB), or resistant to other first-line or second-line TB medicines. In WHO guidelines and reports, MDR-TB and RR-TB cases are often grouped together as MDR/RR-TB and are eligible for treatment with MDR-TB regimens [16].

The new definitions of pre-XDR-TB and XDR-TB are shown in table 2.

Next steps

WHO implemented the new definitions of pre-XDR- and XDR-TB as of January 2021. National TB programmes will need to update their laboratory and surveillance systems to accommodate the new definitions. Updated surveillance systems will allow countries to monitor the situation regarding evolving drug resistance in their contexts, as well as reporting of pre-XDR-TB and XDR-TB to WHO on an annual basis. As second-line line probe assays are available in many countries for fluoroquinolone DST [28], undertaking surveillance for pre-XDR-TB is not expected to pose new obstacles. However, the changes required for the definition of XDR-TB are more complex, requiring a scale-up of laboratory capacity to perform DST for bedaquiline and linezolid, which will likely be based on phenotypic DST initially, as genotypic testing is currently hampered by the limited understanding of the molecular basis of resistance to these drugs. Therefore, these new definitions should trigger a scale up of diagnostic services for drug-resistant TB, particularly for the fluoroquinolones and the group A drugs, but eventually for other second-line drugs. Clinicians, TB programme managers and other stakeholders responsible for treating patients with drug-resistant TB should be made aware of these new definitions and their implications for treatment, surveillance and reporting. The overall aim should be the appropriate treatment of patients to maximise the chance of cure. All of these actions require renewed efforts from the research and development sector, academia, funding agencies, national TB programmes and technical partners, and will ultimately aim to improve the diagnosis and treatment of patients with drug-resistant TB.

TABLE 2 The new definition of pre-XDR-TB and the revised definition of XDR-TB, effective from January 2021

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[#]
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[#] and at least one additional group A drug[¶]

TB: tuberculosis; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; XDR-TB: extensively drug-resistant TB. [#]: the fluoroquinolones include levofloxacin and moxifloxacin, because these are the fluoroquinolones currently recommended by the World Health Organization for inclusion in shorter and longer regimens; [¶]: 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.

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