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

27-29 October 2020

World Health Organization

Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27-29 October 2020

ISBN 978-92-4-001866-2 (electronic version)

ISBN 978-92-4-001867-9 (print version)

Contents

Abbreviations and acronyms ..... **iv**

Executive summary ..... **v**

1. Background and current evidence **1**

1.1 Background and history 1

1.2 Global epidemiology of MDR/RR-TB and XDR-TB 2

1.3 Advances in TB diagnostics and treatment 4

2. Summary of the consultation meeting **7**

2.1 Rationale for the change 7

2.2 Meeting objectives 9

2.3 Setting the scene for a consultation 9

2.4 Operational issues that affect the definition of XDR-TB 15

2.5 Principles to guide the development of a new definition of XDR-TB 17

2.6 Options for a definition of XDR-TB 18

3. Consultation outcomes: the new definitions of pre-XDR-TB and XDR-TB **19**

3.1 Next steps 19

Annex 1: Grouping of medicines recommended for use in longer MDR-TB regimens 23

Annex 2: Possible resistance patterns to second-line drugs in Group A and related treatment regimen options 25

Annex 3: Possible revised definitions of XDR-TB and their potential advantages, disadvantages and implications 26

Annex 4: Algorithm for longer MDR-TB regimen composition in commonplace situations of resistance pattern or contraindication 28

Annex 5: Agenda for the expert consultation meeting on the definition of XDR-TB 30

Annex 6: List of participants for the expert consultation meeting on the definition of XDR-TB 31

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

Globally, 206 030 cases of multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) were detected and notified in 2019, representing 44% of the estimated 465 000 (range, 400 000–535 000) MDR/RR-TB incident cases (14). There is a large detection gap between the estimated number of individuals with MDR/RR-TB and the number reported by national TB programmes (NTPs) to WHO. Closing this large detection gap will require improvements in overall TB case detection, including the proportion of pulmonary cases that are bacteriologically confirmed and the coverage of DST.

A total of 13 068 cases of XDR-TB were reported by 81 countries in 2018, with 88% of cases being from the WHO European Region (7889) and the WHO South-East Asia Region (3580) (5). The

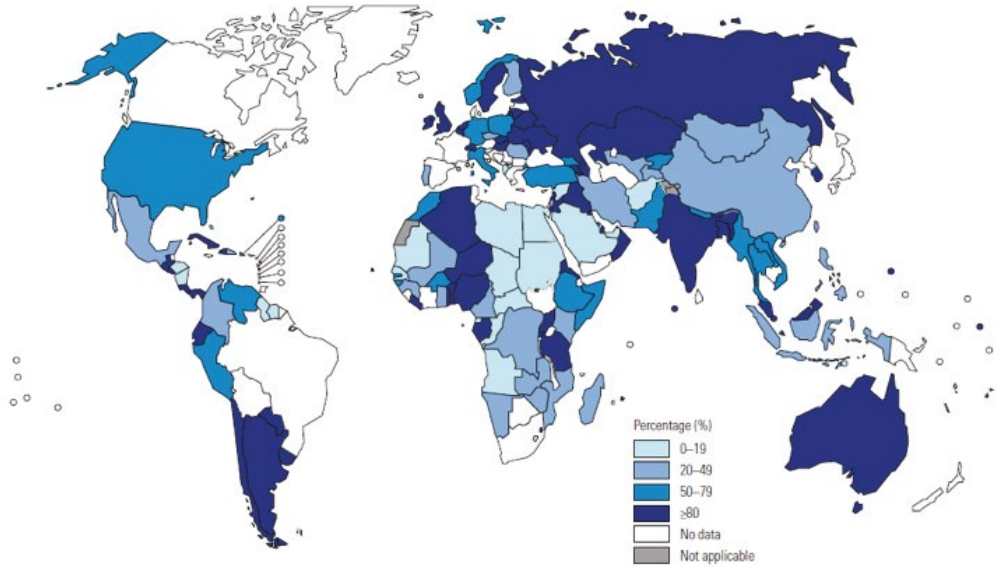
1 The seven-point plan included four short-term actions: the development of emergency response plans, rapid surveys to identify the magnitude of the problem, strengthening and expanding laboratory capacity, and infection control measures; and three long-term actions: establish capacity for clinical and public health managers to respond, promote universal access to antiretroviral therapy for all TB patients living with HIV/AIDS, and support and increase funding for research into the development of new anti-TB drugs and rapid diagnostic tests for MDR-TB and XDR-TB.

five countries that reported the largest numbers of cases of XDR-TB in 2018 were Belarus, India, the Russian Federation, South Africa and Ukraine (5). Not all patients diagnosed with XDR-TB were able to access treatment in 2018; globally, 11 403 patients with XDR-TB were enrolled in treatment in 78 countries and territories (87%), a 16% increase compared with 2017 (5). In 26 of these countries, the number of XDR-TB cases enrolled in treatment was less than the number notified (5).

1.2.2 Coverage with second-line DST

Diagnosing drug resistance, including XDR-TB, relies on access to second-line (SL) DST, preferably carried out in laboratories that are subject to rigorous and standardized quality assurance measures. Overall, in 2019, 57% of pulmonary TB cases were bacteriologically confirmed, a slight increase from 55% in 2018 (5). Of these bacteriologically confirmed pulmonary TB cases, 61% were tested for rifampicin resistance, an increase from 51% in 2018 (5). DST coverage for these patients was 59% for new and 80% for previously treated TB patients (5). Among MDR/RR-TB patients notified in 2019, 71% were tested for resistance to fluoroquinolones; in 2018, 59% were tested for resistance to both fluoroquinolones and SL injectable agents, a considerable increase from the 49% tested in 2017. Coverage for SL DST varied widely among countries (see Fig. 1) (5).

Fig. 1. Percentage of MDR/RR-TB cases tested for susceptibility to fluoroquinolones, 2019
Source: WHO, 2020.



MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; WHO: World Health Organization.

1.2.3 Treatment outcomes for patients with MDR/RR-TB and XDR-TB

A total of 146 countries and territories reported treatment outcomes for people started on MDR-TB treatment in 2017 (5). Although the proportion of MDR/RR-TB patients in the 2017 cohort who successfully completed treatment (i.e. who were cured or completed treatment) was 57%, the figure was only 44% for patients with MDR-TB and additional fluoroquinolone resistance. Among 9258 patients started on treatment for XDR-TB in 2016, in 57 countries and territories for which outcomes were reported, 39% completed treatment successfully, 26% died, treatment failed for 18%, and 18% were lost to follow-up or their treatment outcome was not evaluated (5). India, the

Russian Federation and Ukraine accounted for 84% of the 2016 XDR-TB cohort (5). Among seven countries with XDR-TB cohorts of more than 100 individuals, mortality was highest in India (at 41%) and Uzbekistan (at 26%) (5). It is also worth noting that there has been no significant improvement in treatment outcomes in these groups of patients over the past 5 years.

1.3 Advances in TB diagnostics and treatment

1.3.1 Updates on new medicines and the WHO DR-TB treatment guidelines

In 1996–1997, when the first DR-TB treatment guidelines were issued, a ranking of medicines by descending order of perceived effectiveness was produced, to guide the construct of MDR-TB treatment regimens under normal programmatic conditions (6). This list was restructured in 2006 (7), and again in 2016 (15) and 2018 (16), as evidence of the effectiveness and safety of medicines accrued. These changes reflect important contemporary developments; namely, the advent of new agents for MDR-TB (e.g. bedaquiline and delamanid), the increasing use of repurposed medicines for MDR-TB (e.g. carbapenems, clofazimine, linezolid and moxifloxacin), the withdrawal of agents from the market (e.g. gatifloxacin and thioacetazone), and the declining importance of certain medicines as more effective and safer options become available (e.g. the injectable agents, *p*-aminosalicylic acid and the thioamides).

Since 2013, two new TB medicines, bedaquiline and delamanid, have been assessed and recommended by WHO for use in MDR-TB treatment (17). These two compounds have been found to be effective for treatment of TB after almost a half century without any new TB medicines.

In 2016, WHO introduced a conditional recommendation for a shorter, 9–11-month standardized regimen (referred to as "Bangladesh") for the treatment of MDR/RR-TB without resistance to injectable agents, fluoroquinolones or other agents making up the regimen (this regimen comprises 4–6 Km-Mfx-Cfz-Pto(Eto)-Hh-E-Z / 5 Mfx-Cfz-E-Z) (15). It was considered important to have access to rapid testing for resistance to the aminoglycosides and fluoroquinolones (e.g. line probe assays [LPAs]) before starting this treatment. The composition of the medicines in the shorter regimen has evolved over time, based on the results of emerging research that has tested the effectiveness and safety of shorter regimens for MDR-TB.

In 2018, the classification of medicines used in longer MDR-TB treatment regimens was revised following the evidence-informed update of the WHO guidelines on DR-TB treatment (16). This new classification is based on drug class, and level of certainty in the evidence on effectiveness and safety (i.e. balance between benefits and risk of harm). TB medicines to be used for the treatment of MDR/RR-TB are categorized into Groups A, B and C; these groups feature the medicines to be used to compose longer MDR-TB regimens, where possible, given in order of priority (Annex 1). With the new classification, three drugs in Group A – bedaquiline, the fluoroquinolones (levofloxacin or moxifloxacin) and linezolid – are considered top priority for the composition of a longer MDR-TB regimen, whenever such a regimen is possible. The new classification of TB medicines has facilitated the composition of all-oral longer regimens that have been recommended as a preferred option over longer, injectable-based regimens. Amikacin (or streptomycin) is the only injectable agent included in Group C as part of the longer regimens. Kanamycin and capreomycin are no longer recommended for MDR-TB treatment because of their association with poorer treatment outcomes when compared with other SLDs used for the treatment of DR-TB (18).

The updated WHO 2020 guidelines (18) recommend an all-oral bedaquiline-based shorter regimen in place of the previously recommended injectable-based shorter regimen, with one of the key eligibility criteria being that patients are not resistant to the fluoroquinolones. The shorter regimen comprises (6 Bdq plus 4–6 Lfx/ Mfx-Cfz-Eto-)-Hh-E-Z / 5 Lfx/Mfx-Cfz-E-Z.

All-oral regimens, either shorter or longer, can be offered to MDR/RR-TB patients in most cases, depending on resistance to fluoroquinolones, other SLDs and various eligibility criteria. With the 2020 guideline update, the use of injectable agents is limited to a small number of patients receiving longer regimens, who have limited treatment options and for whom it would not otherwise be possible to compose an all-oral longer regimen.

The WHO 2020 guidelines also recommend a 6–9-month regimen that comprises a new medicine, pretomanid, together with bedaquiline and linezolid (i.e. the BPaL regimen) for the treatment of MDR-TB with additional resistance to fluoroquinolones; however, this regimen is to be used under operational research conditions only.

1.3.2 Updates of the WHO guidance on TB diagnostics and DST

Rapid molecular testing is making it increasingly feasible for NTPs to detect MDR/RR-TB and other types of resistance, and to use the results to guide treatment decisions (19). Hence, rapid molecular testing should be available and accessible, to allow for genotypic DST (gDST) for at least rifampicin and fluoroquinolones, given that DST for both of these agents is essential for selecting the most appropriate initial regimen. WHO recommends the use of the approved rapid molecular DST as the initial test to detect rifampicin resistance before the initiation of appropriate therapy for all TB patients, including new patients and those with a previous history of TB treatment (20). The assays currently endorsed for this purpose are Xpert MTB/RIF®, Xpert MTB/RIF® Ultra and Truenat MTB-RIF Dx (16). The increased recognition of drug resistance and improved access to rapid molecular testing have led more programmes to test for at least rifampicin resistance at the start of TB treatment. In addition to detection of rifampicin resistance, an LPA can detect mutations commonly associated with resistance to rifampicin, isoniazid, fluoroquinolones and SL injectable agents.

Results from LPAs typically become available within a few days of testing; thus, they can be used to decide on the initial regimen for treatment of isoniazid-resistant TB (Hr-TB), or some other forms of mono-resistant or poly-resistant TB. Apart from their rapidity, LPAs can provide information on mutation patterns, which can influence the choice of treatment. For example, if the only mutation present is the inhA, it is likely that isoniazid can still be effective at high dose; in contrast, if the katG mutation alone or both inhA and katG are present, isoniazid is no longer effective, even at high dose. If rifampicin resistance is detected, rapid molecular tests for resistance to isoniazid and fluoroquinolones should be performed promptly, to inform the decision on which regimen to use for the treatment (20). Rapid molecular testing for both rifampicin and fluoroquinolones is widely available; countries have accumulated experience in using such tests, and access is also supported by the main donors where necessary. Commercially available rapid molecular methods (e.g. the SL LPAs) detect about 85% of fluoroquinolone-resistant isolates (19). Culture-based DST for fluoroquinolones should be considered when the prevalence of resistance to these drugs is high, or when resistance is suspected despite the molecular tests being negative.

The pipeline for molecular diagnostics is expanding; however, most of these are designed for the drugs that are already covered by existing assays and are not endorsed currently. Centralized platforms (Abbott RealTime MTB and MTB-RIF/INH assays, Roche cobas® MTB and MTB-RIF/INH assays, Hain FluoroType® MTBDR assay and BD MAX™ MDR-TB assay) detect resistance within the resistance-determining genotypic regions for rifampicin and isoniazid. The Genoscholar® PZA-TB II assay (Nipro, Osaka, Japan) is the only commercially available assay for the detection of mutations within the *pncA* gene (including the promoter region) that are likely to lead to pyrazinamide resistance. Fluoroquinolone resistance detection assays that are emerging are the cartridge-based Xpert MTB/XDR (Cepheid) and similar products from Molbio and Bioneer.

A new promising class of diagnostics with potential to fulfil the need for comprehensive universal gDST uses next-generation sequencing (NGS) technology. Targeted NGS assays have the potential

to detect genetic determinants of resistance to new and repurposed drugs, and are thus an important advancement in drug resistance determination. However, the knowledge base to interpret these data is sparse; hence, these assays are of limited value currently, but have great potential for the future.

Phenotypic DST (pDST) is the reference standard for drug resistance determination; however, it is slow and requires specialized skills and infrastructure. It has been progressively replaced by molecular assays for core first-line drugs and SLDs, and is now reserved for scenarios where resistance is not identified despite a high pretest probability, or to resolve discordance. However, pDST remains important for detection of resistance to new and repurposed drugs, and to drugs for which molecular determinants are poorly described. Updated critical concentration criteria have been published for bedaquiline, clofazimine, delamanid, fluoroquinolones, linezolid and injectable agents (20). For these drugs, pDST uses existing methods (MGIT960 and Agar Proportion (7H10)) that are widely available and are currently the primary method for resistance determination (21). A standardized DST method for pretomanid is being developed and will be made available in the near future. Capacity to test for at least bedaquiline and linezolid should be established as a high priority; however, while this DST capacity is being established, regimen adoption and implementation (in line with recent WHO recommendations) can proceed. If available, targeted or whole genome sequencing (or sequencing of the *pncA* gene) will be used as a reference method to detect pyrazinamide resistance. Susceptibility to ethionamide/prothionamide may in part be inferred from the results of molecular testing for isoniazid resistance (i.e. presence of mutations in the *inhA* promoter region) using LPA. The use of pDST for cycloserine/terizidone, ethambutol, ethionamide/prothionamide, imipenem/meropenem or *p*-aminosalicylic acid is not routinely recommended because results may be unreliable.

2. Summary of the consultation meeting

2.1 Rationale for the change

2.1.1 Why is the definition of XDR-TB outdated?

XDR-TB was initially defined as MDR-TB with further resistance to three or more of the six main classes of SLDs (at the time, these were defined as the aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine and *p*-aminosalicylic acid) (4). The definition was revised following the first meeting of the WHO Global Task Force on XDR-TB, in October 2006. Revision of the definition took into consideration several programmatic and clinical considerations, based on the available knowledge at that time, including feasibility and reproducibility of DST for SLDs, efficacy and availability of SLDs, and differences in treatment outcomes. The importance of the drastically different treatment outcomes in the case of resistance to the fluoroquinolones was reinforced by several studies (22, 23) based on an individual patient dataset available in 2012–13.

Further revision of the XDR-TB definition will also need to consider these prominent aspects. In addition, a revised definition should be:

- straightforward and succinct;
- useful for defining the group of TB patients who will require a significantly different treatment approach in order to attain better treatment outcomes, implemented in a timely manner ; and
- able to be adopted for use in surveillance and epidemiological reporting, to flag the seriousness of the situation and to act as a measure of progress.

The 2020 WHO guidelines on DR-TB treatment have almost completely phased out the use of injectable drugs in all of the recommended treatment regimens, longer or shorter (18). In particular, injectable agents are no longer recommended as part of the shorter regimen that is now an all-oral bedaquiline-containing regimen and has largely been standardized. In the priority classification of SLDs recommended when designing individualized longer regimens, injectable agents have been deprioritized to Group C; only two of these agents (amikacin and streptomycin) have been retained, but with a number of caveats and with their use only recommended when no sufficient drugs in Groups A and B can be obtained to design an effective regimen.

In summary, with the changes in the diagnostic and treatment recommendations, the following points can be made about the 2006 definition of XDR-TB:

- The 2006 definition 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.

The revised XDR-TB definition will therefore need to:

- consider the key role of fluoroquinolones in the treatment of MDR/RR-TB;
- disregard the SL injectable agents because they now have a diminished role in the treatment of DR-TB;
- take into consideration the important role of the new or repurposed drugs in Group A as part of the longer regimens – in particular, bedaquiline and linezolid, acknowledging that bedaquiline features as a priority medicine in both the longer and shorter regimens, and that both bedaquiline and linezolid are included in the BPaL regimen;
- take into consideration the rapid DST and sequencing methods already available, or those expected to be available in the next few years (e.g. rapid gDST for rifampicin, isoniazid, ethionamide and the fluoroquinolones; and slower pDST for bedaquiline and linezolid [and potentially for pretomanid]);
- be feasible for implementation by NTPs when undertaking TB surveillance activities, and for epidemiological assessment of the country or global situation and progress review;
- be practical and useful for taking clinical decisions and when deciding on eligibility while designing treatment regimens; hence, it is critical that the DST required to define it can be realistically scaled up to reach the patients who need treatment, without incurring a significant drain on resources (e.g. potential for price reductions) or creating a bottleneck in the delivery of life-saving treatment until the capacity to conduct this testing becomes available;
- identify a resistance pattern that signals the need for an important change in the treatment options that is otherwise recommended for MDR/RR-TB patients without that form of resistance; and
- take into consideration current knowledge on the prevalence of resistance to SLDs obtained through drug-resistance surveys or other surveys, and as part of routine surveillance.

2.1.2 Possible options for a revised definition

Based on the discussion above, several options were considered for the revision of the XDR-TB definition and were presented to participants in the concept note for the consultation. These possible options were tentative – the aim was to frame the discussion during the consultation. The options considered were:

- replacing the current XDR-TB definition with a definition that would feature only fluoroquinolone-resistant TB in addition to MDR/RR-TB;
- including resistance to the fluoroquinolones and bedaquiline[2], in addition to MDR/RR-TB, under the new XDR-TB definition;
- including resistance to the fluoroquinolones and linezolid, in addition to MDR/RR-TB, under the new XDR-TB definition;
- including resistance to the fluoroquinolones, bedaquiline **and** linezolid, in addition to MDR/RR-TB, under the new XDR-TB definition; or
- including resistance to any two Group A medicines, in addition to MDR/RR-TB, under the new XDR-TB definition.

2 Bedaquiline was considered a key drug (in addition to the fluoroquinolones and linezolid) because it is a Group A medicine for use in longer regimens and is also included in both shorter and longer regimens, in the BPaL regimen and in other regimens for the treatment of DR-TB that are currently being examined in Phase III trials.

Other possible definitions (see Annex 3) could have included various drug-resistance patterns; for example, resistance to bedaquiline and linezolid but not to fluoroquinolone (in addition to MDR/RR-TB), or resistance to linezolid only (in addition to MDR/RR-TB). However, because those particular resistances are currently rare (24, 25), not all potential possibilities were included in the concept note.

The advantages, disadvantages and potential implications for these options are presented in Annex 3. Possible treatment options, aligned with the summary algorithm for the composition of longer MDR-TB regimens, are reproduced from Module 4 of the WHO operational handbook on TB (see Annex 4) (26).

2.2 Meeting objectives

The overall goal of this consultation was to bring together representatives from NTPs, implementing partners, patient representatives, funding agencies and other key stakeholders, to discuss recent changes in treatment regimens and diagnostics for DR-TB, and to determine how these impact on the definition of XDR-TB, with a view to revising this definition.

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.

2.3 Setting the scene for a consultation

Participants at the consultation were provided with a concept note before the meeting (reproduced in Sections 1-4 of this report). The consultation consisted of three online meetings held via Zoom over three consecutive afternoons (see Annex 5 for the agenda). The list of participants for this meeting (given in Annex 6) reflected a diverse range of stakeholders and end users from several relevant sectors, including representatives from high TB and MDR-TB burden countries, NTP managers, clinicians, researchers, academics, donors, partner technical organizations, other relevant WHO departments and civil society. Declarations of interest were sought from selected participants according to the requirements of WHO's *Guidelines for declaration of interests* policy. In addition to the information contained in the concept note, on Day 1 of the meeting there were four brief presentations; these were designed to provide background information relevant to the current and possible future definitions of XDR-TB. The remainder of the meeting was devoted to discussion.

Dr Tereza Kasaeva, Director of the WHO Global TB Programme, opened the meeting by welcoming all meeting participants and thanking them for their eager interest in the theme of the consultation. She stated that this consultation was very timely and she emphasized the need to consider a new definition of XDR-TB, given recent developments in the diagnosis and treatment of DR-TB. The current definition of XDR-TB was produced at a WHO-convened meeting of the WHO Global Task Force on XDR-TB in 2006. Since then, there have been many new developments in the management of DR-TB, including the lowered priority of the injectable agents in the treatment of DR-TB, which are part of the current XDR-TB definition.

Based on data provided to WHO by Member States and subsequently published in the *Global tuberculosis report 2020* (27), **Dr Fuad Mirzayev, WHO Global TB Programme**, outlined the latest data on XDR-TB, and WHO recommendations on the treatment of MDR-TB and XDR-TB. Based on these data, it is evident that case detection for DR-TB in general is suboptimal, with only about 45% of all MDR-TB cases being notified. In 2019, almost 13 000 patients with XDR-TB were enrolled in treatment, but treatment success for this patient group remains below 50%. The current WHO recommendations on the treatment of DR-TB include a shorter regimen (which is standardized) or a longer regimen (which is individualized), and an additional regimen used for patients with XDR-TB, recommended under operational research conditions only (i.e. the BPaL regimen, comprising bedaquiline, pretomanid and linezolid).[3] Most regimens that can be designed under these possible options do not require use of injectable agents and are further described in Fig. 2 below. Dr Mirzayev also highlighted a clear trend towards shorter and all-oral regimens for treatment of DR-TB, given the pipeline of Phase III clinical trials that are ongoing. Currently, the longer regimen for the treatment of DR-TB designates the injectable agents as much lower priority medicines than they were previously, and does not include these agents in the shorter regimen.

Dr Mirzayev concluded his presentation by noting some of the major issues with the current definition of XDR-TB:

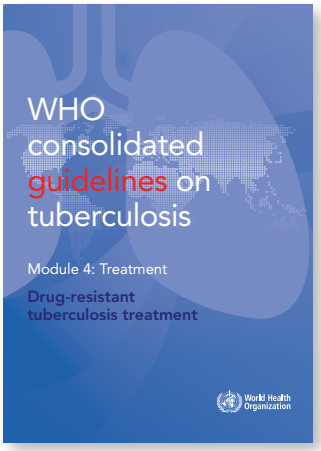
- SL injectable agents have lost their priority ranking, and have been replaced by other, more effective oral agents;
- fluoroquinolone resistance is linked to a decline in favourable treatment outcomes, and leads to an important choice between either the shorter or longer regimens (or operational research); and
- resistance to bedaquiline and linezolid is not reflected in the current definition (both types of resistance are rare, but they exist, and monitoring for resistance to both drugs is important given the current composition of regimens).

Fig. 2. WHO recommendations on the treatment of DR-TB and XDR-TB.
***Source: WHO* (18)**

All patients with MDR/RR-TB, including those with additional resistance to fluoroquinolones, may benefit from effective all-oral treatment regimens, shorter or longer.

1. For MDR/RR-TB patients without previous exposure to second-line treatment and bedaquiline, without fluoroquinolone resistance and no extensive TB disease or severe extrapulmonary TB, the preferred treatment option is a **shorter, all-oral, bedaquiline-containing regimen**. In this group of patients, national programmes can phase out use of the injectable-containing shorter regimen.

2. For MDR/RR-TB patients with extensive TB disease, severe forms of extrapulmonary TB, those with resistance to fluoroquinolones or who have been exposed to treatment with second-line drugs will benefit from an **individualized longer regimen** designed using the priority grouping of medicines.



3. Novel BPaL regimen for MDR-TB with additional quinolone resistance under operational research conditions.

BPaL: bedaquiline, pretomanid and linezolid; DR-TB: drug-resistant tuberculosis; MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; TB: tuberculosis; WHO: World Health Organization; XDR-TB: extensively drug-resistant tuberculosis.

3 See WHO 2020 (18) for the most recent recommendations on the treatment of DR-TB.

Dr Nazir Ismail, WHO Global TB Programme, provided an overview of current and historical WHO recommendations on TB diagnostics and DST[4], as well as future directions in this area. The latest WHO guidelines on TB diagnostics, published in June 2020, include recommendations on molecular assays as the initial diagnostic test for the diagnosis of pulmonary TB and detection of rifampicin resistance (20). Recommendations for first-line and SL LPA testing are also included in these guidelines (covering isoniazid, the fluoroquinolones and the SL injectable agents).

Criteria for pDST have been established for key new and repurposed drugs, including bedaquiline, delamanid, clofazimine, linezolid, levofloxacin and moxifloxacin (with a clinical breakpoint and critical concentration established for moxifloxacin). Updated criteria for pDST for rifampicin and isoniazid are in progress, and will soon be released by WHO. In 2018, WHO also published technical documents on critical concentrations for DST, the use of NGS for the detection of mutations associated with drug-resistant *Mycobacterium tuberculosis* and a technical manual for DST of medicines used in the treatment of TB (21, 28-30).

In December 2020, a WHO-convened Guideline Development Group will assess the evidence for several diagnostic tests, including:

- centralized assays that present end-to-end solutions for the detection of TB and resistance to rifampicin and isoniazid;
- cartridge-based technology for the detection of resistance to isoniazid and SLDs, including a predictor for ethionamide, the fluoroquinolones and SL injectable drugs; and
- hybridization-based technology (LPA) to detect pyrazinamide resistance.

WHO is also in the process of updating the catalogue of drug mutations, which will be published in 2021.

Looking further into the future, there is a potential role for additional diagnostic technologies such as NGS (targeted and whole genome), including for bedaquiline/clofazimine (*rv0678*) and linezolid (*rrl* and *rplc*). Microtitre plates developed by Thermo Fisher offer another option for pDST, and these could be used for the first-line drugs and Group A and Group B drugs; however, because they are phenotypic, they are based on culture.

Table 1 summarizes the spectrum of TB diagnostic tools, including whether they are currently endorsed by WHO or whether there is the possibility of future endorsement.

4 The most recent recommendations on the diagnosis of TB are available in WHO 2020 (20).

Table 1. The spectrum of current and future TB diagnostics, including endorsement status by WHO (currently endorsed or not currently endorsed but endorsement planned)

Grouping of medicines	Medicine	CB	E2E	LPA	tNGS	WGS	pDST	pBMD
First line	RIF	X	Z	X	Z	Z	X	Z
	INH	Z	Z	X	Z	Z	X	Z
	EMB				Z	Z	X	Z
	PZA			Z	Z	Z	X	Z
Group A	LFX/	Z		X	Z	Z	X	Z
	MFX	Z		X	Z	Z	X	Z
	BDQ				Z	Z	X	Z
	LZD				Z	Z	X	Z
Group B	CFZ				Z	Z	X	Z
	DCS							
Group C	DLM				Z	Z	X	Z
	IMP-CLN/							
	MPM							
	AMK	Z		X	Z	Z	X	Z
	STR				Z	Z	X	Z
	ETO/				Z	Z	X	
	PTO				Z	Z	X	
	PAS							

AMK: amikacin; BDQ: bedaquiline; CB: Cartridge based nucleic acid amplification tests (e.g. Xpert and TrueNAT platforms); CLN: cilastatin; DCS: D-cycloserine; DLM: delamanid; EMB: ethambutol; ETO: ethionamide; E2E: fully automated end-to-end solutions; IMP: imipenem; INH: isoniazid; LFX: levofloxacin; LPA: line probe assay; LZD: linezolid; MFX: moxifloxacin; MPM: meropenem; PAS: para-aminosalicylic acid; pBMD: phenotypic broth microdilution DST; pDST: phenotypic drug-susceptibility testing (Agar and MGIT960); PTO: prothionamide; PZA: pyrazinamide; RIF: rifampicin; STR: streptomycin; TB: tuberculosis; tNGS: targeted next-generation sequencing; WGS: whole genome sequencing; WHO: World Health Organization.
X – endorsed, Z – not currently endorsed, but endorsement is planned.

Dr Anna Dean, WHO Global TB Programme, spoke about the most recent surveillance data that have been reported to WHO, the majority of which have been published in the *Global tuberculosis report 2020* (27). These data highlight that the two main methods of surveillance for DR-TB globally are routine surveillance (data entered into a national surveillance system) or national anti-TB drug resistance ad hoc surveys. Global data captured from routine surveillance consist of results from testing isolates for rifampicin among bacteriologically confirmed pulmonary TB cases (new and previously treated), and then testing for resistance to fluoroquinolones among those with confirmed rifampicin-resistant TB (RR-TB). In national surveys, DST depends on laboratory capacity, the diagnostic algorithm being used and the resources available.

High-quality data on rifampicin resistance have improved globally over time; such data are defined as rifampicin testing for at least 80% of cases of new bacteriologically confirmed pulmonary TB cases. A total of 86 Member States reported high-quality data on rifampicin resistance in 2014, and this rose to 125 Member States in 2019. The increase has mainly been attributed to the roll-out of rapid molecular testing (mostly Xpert MTB/RIF). In addition, when it comes to fluoroquinolone resistance, 91 Member States had high-quality data; that is, at least 80% DST coverage for rifampicin among patients with new bacteriologically confirmed pulmonary TB, and at least 80% DST coverage for fluoroquinolone testing among those with confirmed RR-TB. From routine surveillance data, in 2019, 71% of RR-TB cases had DST for fluoroquinolones, but only 44% of RR-TB cases were detected. To conclude, Dr Dean highlighted that generating representative data on drug resistance for public health action requires:

- a high level of bacteriological confirmation among TB cases;
- good coverage of rifampicin testing among bacteriologically confirmed TB cases; and
- good coverage of testing for combinations of SLDs among RR-TB cases.

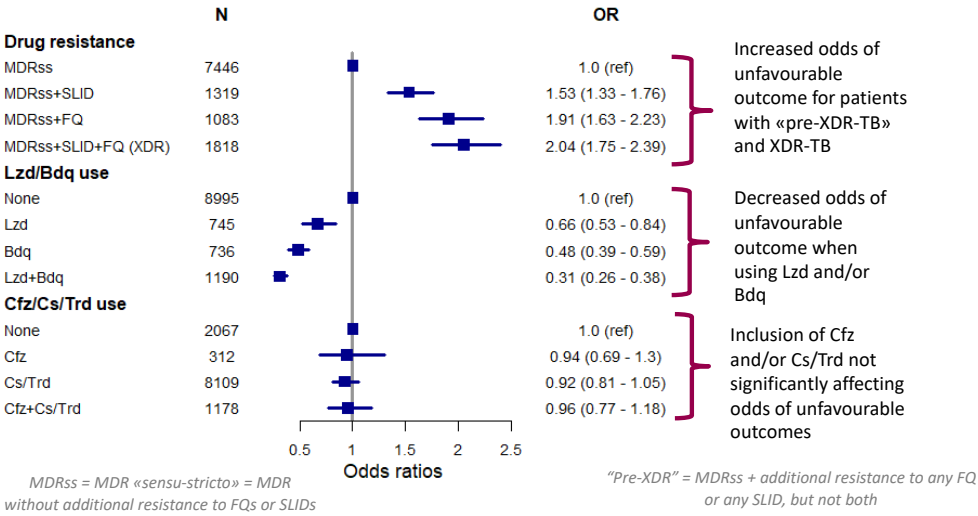
Dr Maroussia Roelens, Institute of Global Health, University of Geneva, presented the results of a study designed to assess whether the existing definitions for MDR-TB and XDR-TB (including for the informal "pre-XDR-TB"[5]) remain adequate to identify different levels of disease severity or for clinical management, in view of the recent changes in WHO treatment recommendations. Based on data from the individual patient dataset on the treatment of DR-TB (hosted at McGill University), and using a logistic regression approach, the researchers assessed treatment outcomes for patients with MDR-TB and XDR-TB exposed to longer regimens containing different priority TB medicines. The researchers found that patients with pre-XDR-TB were at greater risk of an unfavourable outcome (i.e. treatment failure, relapse, death or loss to follow-up) compared with patients with MDR-TB in the strict sense of the definition, with the odds of an unfavourable outcome being slightly higher for patients with resistance to the fluoroquinolones (odds ratio [OR]: 1.91, 95% confidence interval [CI]: 1.63–2.23) than for patients with resistance to SL injectable agents (OR: 1.53, 95% CI: 1.33–1.76). Similar findings were shown for patients with XDR-TB (OR: 2.04, 95% CI: 1.75–2.39) compared with patients with MDR-TB.

The use of linezolid or bedaquiline (or both) was associated with lower odds of an unfavourable outcome compared with patients taking neither of these drugs. This was particularly evident when both drugs were combined (OR: 0.31, 95% CI: 0.26–0.38; compared with OR: 0.66, 95% CI: 0.53–0.84 for linezolid only; and OR: 0.48, 95% CI: 0.39–0.59 for bedaquiline only) (Fig. 3). The inclusion of clofazimine or cycloserine/terizidone (or both) did not seem to significantly affect the odds of a successful outcome (OR: 0.94, 95% CI: 0.69–1.30 for clofazimine only; OR: 0.92, 95% CI: 0.81–1.05 for cycloserine/terizidone only; and OR: 0.96, 95% CI: 0.77–1.18 for both, compared with none) (Fig. 3). Similar to the combined analysis, in the subgroup of patients who received neither linezolid nor bedaquiline, the odds of an unfavourable outcome were increased for pre-XDR-TB and XDR-TB compared with MDR-TB (OR: 2.08, 95% CI: 1.71–2.54 for MDR-TB + fluoroquinolone; OR: 1.65, 95% CI: 1.41–1.94 for MDR-TB + SL injectable agent; and OR: 3.28, 95% CI: 2.61–4.11 for XDR-TB) (Fig. 4). Based on this analysis, the researchers concluded that pre-XDR-TB and XDR-TB could be defined by modulating different levels of resistance to Group A drugs.

5 Manquant

Fig. 3. Association with drug-resistance patterns and unfavourable treatment outcomes, stratified by regimens that include linezolid, bedaquiline, clofazimine, cycloserine and terizidone

Source: Roelens M et al., unpublished data submitted for publication, 2020.



Bdq: bedaquiline; Cfz: clofazimine; Cs: cycloserine; FQ: fluoroquinolone; Lzd: linezolid; MDR: multidrug resistant; MDRss: multidrug-resistant sensu stricto; N: number; OR: odds ratio; SLID: second-line injectable drug; TB: tuberculosis; Trd; terizidone; XDR: extensively drug resistant.

Fig. 4. Association with regimens that contain linezolid or bedaquiline (or both) and unfavourable treatment outcomes, stratified by drug-resistance patterns

Source: Roelens M et al., unpublished data submitted for publication, 2020.

		No Lzd/Bdq use (N = 8995)	Use Lzd only (N = 745)	Use Bdq only (N = 736)	Use Lzd + Bdq (N = 1190)
Drug resistance pattern		P < 0.001	P = 0.42	P = 0.23	P = 0.26
	MDRss	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	MDRss + FQ	2.08 (1.71–2.54)	0.97 (0.55–1.71)	1.04 (0.64–1.69)	1.16 (0.76–1.78)
	MDRss + SLID	1.65 (1.41–1.94)	0.66 (0.37–1.17)	1.38 (0.82–2.31)	0.75 (0.48–1.18)
	XDR	3.28 (2.61–4.11)	0.76 (0.44–1.32)	1.57 (0.98–2.53)	0.89 (0.62–1.28)

Similar to analysis without stratification

Provided Lzd/Bdq used, similar treatment outcomes for all DR patterns

Bdq: bedaquiline; DR: drug resistance; FQ: fluoroquinolone; Lzd: linezolid; MDRss: multidrug-resistant sensu stricto; N: number; SLID: second-line injectable drug; TB: tuberculosis; XDR: extensively drug resistant.

2.4 Operational issues that affect the definition of XDR-TB

The remainder of the meeting on Day 1 included time for discussion about the purpose, principles and operational issues that are important and relevant when thinking about a revised definition of XDR-TB. Most participants suggested that the definition should be updated and changed, bearing in mind the rationale for a change in the definition that had been discussed earlier and recognized the value of retaining the term XDR-TB, because it has had a particular importance and impact in the area of communication and advocacy since it was developed, and it is now well recognized and understood.

The participants also discussed whose needs are served by re-defining XDR-TB. Depending on the perspective taken, the definition of XDR-TB may have a different value, purpose or importance. For example, individual clinicians may feel that a definition is not required for them to deliver appropriate clinical care to a patient, because they will rely on other factors to make clinical decisions (e.g. the DST pattern of the isolate). On the other hand, the definition may be extremely useful for programme managers who want to understand local epidemiological trends, including emerging drug-resistance patterns and their impact on patient outcomes at a population level. Balancing the needs and perspectives of various stakeholders and end users was viewed as difficult, but necessary. This led to a discussion about various challenges that might exist when developing a new definition of XDR-TB, such as:

- the application of the definition of XDR-TB for surveillance purposes versus other purposes (e.g. clinical decision-making);
- the need for nomenclature for various forms of DR-TB versus the need for a prognostic hierarchy that can predict poor treatment outcomes;
- the need for a simple definition versus the potential for it to be more complex and potentially more informative but more difficult to implement; and
- pragmatism versus technicality.

Participants also discussed several operational and implementation issues that affect the definition of XDR-TB.

The participants highlighted that the treatment landscape has changed significantly over the past 10–15 years. In addition, the current research landscape includes a number of trials for the treatment of DR-TB, as well as drug-susceptible TB. For example, the results from the recent study on shortened treatment for drug-susceptible TB (i.e. TBTC 31/ A5349) indicate that drugs that have been traditionally regarded as SLDs (e.g. the fluoroquinolones) may be used for patients with drug-susceptible TB in the future, potentially blurring the lines between what have traditionally been called first-line TB drugs and SLDs. Other issues relevant to treatment include the fact that, in the future, the medicines in Groups A, B and C may change or the groups may include new drugs. Hence, participants felt there was a need to look to the future when re-defining XDR-TB, to ensure that any definition would stand the test of time, and to consider both current WHO recommendations for the treatment of DR-TB and regimens or medicines that are in the pipeline (many of which centre on bedaquiline).

The participants highlighted that the definition of XDR-TB should signal an extremely serious form of TB that is difficult to treat and should also triage patients to the most appropriate treatment regimen. Based on the evidence in the literature, clinical experience, the priority grouping of medicines contained in the current WHO guidelines for longer regimens and potential future regimens, participants felt that TB that is resistant to fluoroquinolones or to Group A drugs (or both), in particular, signal a serious form of TB with the potential for poor treatment outcomes, including death.

Currently, it also signals which patients are eligible for the shorter rather than the longer regimen. Participants also highlighted that the definition should also allow patients to move to a treatment regimen that is most appropriate for them. Ideally, the definition would need to meet both clinical and surveillance purposes because, without surveillance, programme managers and others cannot identify changing epidemiological trends, which has "knock on" effects (e.g. where emerging surveillance trends might stimulate drug development or further roll-out of DST).

The availability of DST was another major concern for meeting participants, because access to available DST methods for some Group A and Group B drugs is currently limited to reference laboratories (especially for bedaquiline, clofazimine and linezolid), whereas rapid DST for the fluoroquinolones is more widely available. Participants were concerned that any definition of XDR-TB needed to take into account future and current treatment regimens, but they also noted that it is crucial to develop and to widely implement rapid DST methods for the Group A and B medicines. A new definition of XDR-TB that includes another Group A drug in addition to a fluoroquinolone may actually stimulate further development of tools to monitor drug resistance for the highest priority, most effective SL medicines. Participants also noted that, although resistance to bedaquiline and linezolid is currently low, there is a need to be vigilant with regard to acquired drug resistance. Therefore, one of the key outcomes of this discussion was that the definition of XDR-TB should stimulate expanded use of DST, particularly for the fluoroquinolones and other Group A drugs.

Related to clinical management was the perceived relative importance of SL medicines. Participants highlighted that fluoroquinolone resistance is extremely important because it signals poor treatment outcomes. In addition, DST is currently available and is recommended by WHO. Bedaquiline and linezolid resistance were also viewed as being important, given their current position as a Group A drugs, their inclusion in the BPaL regimen and potential for inclusion in future regimens. With regard to SL medicines, four main points arose from the discussion:

- the definition of XDR-TB should no longer include reference to injectable agents, given that their use is expected to be minimal in the future;
- the most important SLDs to be considered in the definition of XDR-TB are Group A medicines (i.e. the fluoroquinolones, bedaquiline and linezolid);
- resistance to the fluoroquinolones in addition to MDR/RR-TB needs to be singled out, given the prognostic importance of fluoroquinolone-resistant TB and the fact that it can lead to a choice between treatment regimens for DR-TB; resistance to bedaquiline is also of concern, and access to DST for bedaquiline should be more widely available; and
- there is a need to formalize the definition of pre-XDR-TB (currently defined as MDR-TB plus fluoroquinolone resistance).

From a public health perspective, it was felt that a definition of XDR-TB remains important because it informs aspects of programmatic management (e.g. planning, organization of diagnostic services, procurement of drugs and surveillance). The use of definitions for surveillance was a particular priority, and participants stated that monitoring trends of XDR-TB is crucial, and that this could stimulate the further development of diagnostic tools and drugs.

The patient's perspective was believed to be an important consideration, particularly the fact that the label "XDR-TB" may be associated with stigma. In addition, it was felt that any definition of XDR-TB should not limit access to health care or treatment. Conversely, as mentioned above, a definition of XDR-TB should signal initiation of an appropriate treatment regimen, which is of benefit to patients.

An additional operational challenge discussed was the fact that country regulatory authorities and drug labels indicate whether recently approved drugs that are part of a new regimen are applicable for patients with XDR-TB, which has implications for any revised definition. However, it was also noted that WHO could make regulatory authorities aware of any change in the definition of XDR-TB to facilitate its adoption, without compromising previous regulatory approvals. Finally, it was noted that having labels for MDR-TB and XDR-TB has been useful historically for communication and advocacy purposes. Although not the most important consideration, there may be strategic benefits in retaining the term XDR-TB, especially in the context of national, regional and global targets related to case detection and treatment outcomes for patients with DR-TB, and more broadly in the global antimicrobial resistance agenda.

2.5 Principles to guide the development of a new definition of XDR-TB

Participants discussed several principles that should be borne in mind when thinking about a new definition of XDR-TB. These principles took into account many of the issues discussed on the previous day (e.g. operational and implementation issues) and the need to be clear about the purpose of drafting a new definition (i.e. who it is being drafted for). The revised definition must meet the following criteria:

- **Simple:** It should address the most important needs of stakeholders and end users including NTPs, although it may not be able to address everyone's needs. After extensive discussion about the number of layers or levels of definitions (i.e. how many types of DR-TB there should be beyond MDR-TB), most participants suggested that the definition should have no more than two layers beyond MDR-TB.
- **Measurable:** The new definition should be measurable as a part of routine surveillance. An important underlying principle of surveillance is that the data should be used for public health action, including to guide resource allocation and planning, inform target setting for case-finding of drug resistance among notified TB cases, estimate needs for SLDs, modify national diagnostic algorithms (where relevant), assess appropriateness of treatment regimens and monitor trends in drug resistance over time. In the context of XDR-TB, surveillance is closely related to laboratory capacity to carry out DST for the medicines that are in the definition; however, participants acknowledged that current DST capabilities should not be a limiting factor, nor should potential misclassification (e.g. if there is not the capability to carry out DST for all medicines in the definition at the current time). In the future, XDR-TB should be able to be incorporated into national surveillance systems and reported to WHO.
- **Relevant to programmes, including for surveillance and clinical management:** The new definition should be relevant for the programmatic management of TB, including the fact that it should signal a very serious form of TB and the need for such patients to have a regimen that is different to the regimen for patients with MDR-TB, or other less serious forms of DR-TB.
- **Future-proof:** The new definition should endure for some time into the future. It was acknowledged that it may take some time for countries to adopt the new definition and then be able to measure it. Taking this into account, and acknowledging that it is not helpful for NTPs if definitions change frequently, most participants suggested that any new definition of XDR-TB should be able to endure into the future without the need for change in the medium term.

2.6 Options for a definition of XDR-TB

Based on the operational considerations described above, meeting participants discussed and debated several options for a definition of XDR-TB. They also discussed a formal definition for pre-XDR-TB, raised during discussions on Day 1. The options involved making choices about the structure of the definition, including:

- how many layers or levels the definition should have; that is, whether there should be MDR/RR-TB, pre-XDR-TB, XDR-TB and another more serious form;
- whether the definition should be defined by the inclusion of specific drugs or a group of drugs; that is, whether the definition of XDR-TB should include specific reference to bedaquiline and linezolid, for example, or whether it should refer to Group A drugs without specifying which agent, considering the priority groupings for longer regimens outlined in the current WHO recommendations;
- the number of drugs that should be included in the definition of XDR-TB and the relative importance of these drugs, including the fluoroquinolones, bedaquiline and linezolid;
- nomenclature; that is, what the different levels should be called – for example, whether the nomenclature should:
  - state the number of drugs to which the patient was resistant, rather than using the term XDR-TB per se (e.g. MDR-TB plus 3, MDR-TB plus 4);
  - specifically name the individual drugs to which the strain was resistant (e.g. rifampicin, isoniazid, fluoroquinolone or bedaquiline); or
  - remain as MDR-TB, pre-XDR-TB (informal until now) and XDR-TB.

The pros and cons of these options were discussed at length by the group. Most participants suggested that there should be two layers above MDR-TB, and that the terms MDR-TB, pre-XDR-TB and XDR-TB should be used, acknowledging that the term pre-XDR-TB had not been formally defined in the past but has been used in the literature (31). In addition, both the term and the current definition of MDR/RR-TB should be retained in its current form, meaning that the decision points were on how to define pre-XDR-TB and XDR-TB. The fluoroquinolones and bedaquiline should be considered priority medicines because they belong to Group A medicines and they signal eligibility for the currently recommended shorter regimen (BPaL) under operational research conditions, and that this should be reflected in the definitions.

3. Consultation outcomes: the new definitions of pre-XDR-TB and XDR-TB

Based on the discussions during the consultation, and bearing in mind the agreed principles, WHO proposes a new definition for pre-XDR-TB and the revised definition for XDR-TB, outlined in Box 2. The definition of MDR-TB is unchanged and remains as: TB caused by *Mycobacterium tuberculosis (M. tuberculosis)* strains that are resistant to at least both rifampicin and isoniazid.

For reporting purposes, and also considering that both types of drug resistance require the same treatment options, MDR-TB and RR-TB are often grouped together as MDR/RR-TB. This includes patients with isolates that are resistant to rifampicin only and those that fulfil the definition of MDR-TB.

Box 2. Definition of pre-XDR-TB and updated definition of XDR-TB[a]

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]

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

[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.

3.1 Next steps

WHO will implement the new definitions of pre-XDR and XDR-TB as of January 2021. NTPs will need to orient their laboratory and surveillance systems to accommodate the new definitions. Practically speaking, because SL LPA is available in many countries for fluoroquinolones DST, many countries may be able to undertake surveillance for pre-XDR-TB without major problems. 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. Therefore, these new definitions should trigger a scale up of diagnostic services for DR-TB, particularly for the fluoroquinolones and the Group A drugs, but eventually for other SLDs. This requires 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 DR-TB.

References

1 Tackling drug resistant infections globally: final report and recommendations. Review on antimicrobial resistance. United Kingdom: Government of the United Kingdom; 2016 (https://amr-review.org/).

2 Gupta R, Kim JY, Espinal MA, Caudron JM, Pecoul B, Farmer PE et al. Public health. Responding to market failures in tuberculosis control. Science. 2001;293(5532):1049–51 (https://pubmed.ncbi.nlm.nih.gov/11463877/).

3 WHO TB Supranational Reference Laboratory Network: TB diagnostics and laboratory strengthening [website]. Geneva: World Health Organization; 2020 (https://www.who.int/tb/areas-of-work/laboratory/srl-network/en/).

4 Centers for Disease Control and Prevention (CDC). Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs--worldwide, 2000–2004. MMWR Morb Mortal Wkly Rep. 2006;55(11):301–5 (https://pubmed.ncbi.nlm.nih.gov/16557213/).

5 Shah NS, Wright A, Bai GH, Barrera L, Boulahbal F, Martín-Casabona N et al. Worldwide emergence of extensively drug-resistant tuberculosis. Emerg Infect Dis. 2007;13(3):380–7 (https://pubmed.ncbi.nlm.nih.gov/17552090/).

6 Guidelines for the management of drug-resistant tuberculosis (WHO/TB/96.210 (Rev.1)). Geneva: World Health Organization; 1997 (https://apps.who.int/iris/handle/10665/63465).

7 Guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2006.361). Geneva: World Health Organization; 2006 (https://apps.who.int/iris/bitstream/handle/10665/246249/9789241546959-eng.pdf?sequence=2).

8 Guidelines for the programmatic management of drug-resistant tuberculosis, Emergency update 2008 (WHO/HTM/TB/2008.402). Geneva: World Health Organization; 2008 (https://apps.who.int/iris/bitstream/handle/10665/43965/9789241547581_eng.pdf?sequence=1).

9 Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006;368(9547):1575–80 (https://pubmed.ncbi.nlm.nih.gov/17084757/).

10 World Health Organization. Addressing the threat of tuberculosis caused by extensively drug-resistant Mycobacterium tuberculosis. Wkly Epidemiol Rec. 2006;41(13):386–90 (https://www.who.int/tb/xdr/wer_13oct06/en/).

11 WHO Global Task Force outlines measures to combat XDR-TB worldwide. Geneva: World Health Organization; 2006 (https://www.who.int/mediacentre/news/notes/2006/np29/en/).

12 “Totally drug-resistant” tuberculosis: a WHO consultation on the diagnostic definition and treatment options. Geneva: World Health Organization; 2012 (https://www.who.int/tb/areas-of-work/drug-resistant-tb/xdrconsultation/en/).

13 Report of the meeting of the WHO Global Task Force on XDR-TB. Geneva: World Health Organization; 2006 (https://apps.who.int/iris/handle/10665/69474).

14 Global tuberculosis report 2019. Geneva: World Health Organization; 2019 (https://www.who.int/teams/global-tuberculosis-programme/tb-reports).

15 WHO treatment guidelines for drug-resistant tuberculosis, 2016 update (WHO/HTM/TB/2016.4). Geneva: World Health Organization; 2016 (https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf).

16 WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update (WHO/CDS/TB/2018.15). Geneva: World Health Organization; 2018 (https://www.who.int/tb/areas-of-work/drug-resistant-tb/guideline-update2018/en/).

17 The use of bedaquiline in the treatment of multidrug-resistant tuberculosis. Interim policy guidance (WHO/HTM/TB/2013.6). Geneva: World Health Organization; 2013 (https://www.who.int/tb/publications/mdrtb-treatment-guideline/en/).

18 WHO consolidated guidelines on tuberculosis, Module 4: treatment – drug resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://www.who.int/tb/publications/global_report/en/).

19 The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs: policy guidance (WHO/HTM/TB/2016.07). Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/246131).

20 WHO consolidated guidelines on tuberculosis Module 3: diagnosis – rapid diagnostics for tuberculosis detection. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-3-diagnosis---rapid-diagnostics-for-tuberculosis-detection).

21 Technical report on critical concentrations for TB drug susceptibility testing of medicines used in the treatment of drug-resistant TB. Geneva: World Health Organization; 2018 (https://www.who.int/tb/publications/2018/WHO_technical_report_concentrations_TB_drug_susceptibility/en/).

22 Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox HS, Holtz TH et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. Eur Respir J. 2013;42(1):156–68 (https://pubmed.ncbi.nlm.nih.gov/23100499/).

23 Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017, Ahmad N, Ahuja S, Akkerman O, Alffenaar J, Anderson L et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet. 2018;392(10150):821–34.

24 Pang Y, Zong Z, Huo F, Jing W, Ma Y, Dong L et al. In vitro drug susceptibility of bedaquiline, delamanid, linezolid, clofazimine, moxifloxacin, and gatifloxacin against extensively drug-resistant tuberculosis in Beijing, China. Antimicrob Agents Chemother. 2017;61(10) (https://pubmed.ncbi.nlm.nih.gov/28739779/).

25 Zimenkov DV, Nosova EY, Kulagina EV, Antonova OV, Arslanbaeva LR, Isakova AI et al. Examination of bedaquiline- and linezolid-resistant Mycobacterium tuberculosis isolates from the Moscow region. J Antimicrob Chemother. 2017;72(7):1901–6 (https://pubmed.ncbi.nlm.nih.gov/28387862/).

26 WHO operational handbook on tuberculosis, Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240006997).

27 Global tuberculosis report 2020. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240013131).

28 Technical guide on next-generation sequencing technologies for the detection of mutations associated with drug resistance in Mycobacterium tuberculosis complex. Geneva: World Health Organization; 2018 (https://www.who.int/tb/publications/2018/WHO_technical_guide_nextgen_sequencing/en/).

29 Technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis. Geneva: World Health Organization; 2018 (who.int/tb/publications/2018/WHO_technical_drug_susceptibility_testing/en/).

30 The use of next-generation sequencing technologies for the detection of mutations associated with drug resistance in Mycobacterium tuberculosis complex: technical guide. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/handle/10665/274443).

31 Dheda K, Gumbo T, Maartens G, Dooley KE, McNerney R, Murray M et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. Lancet Respir Med. 2017 (https://pubmed.ncbi.nlm.nih.gov/28344011/).

32 WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis (WHO/HTM/TB/2017.20). Geneva, Switzerland: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/10665/258941/1/WHO-HTM-TB-2017.20-eng.pdf).

Annex 1: Grouping of medicines recommended for use in longer MDR-TB regimensa

Groups & steps	Medicine	
Group A: Include all three medicines	levofloxacin *OR*	Lfx
	moxifloxacin	Mfx
	bedaquiline[b,c]	Bdq
	linezolid[d]	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine *OR*	Cs
	terizidone	Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	delamanid[c,e]	Dlm
	pyrazinamide[f]	Z
	imipenem–cilastatin *OR*	Ipm–Cln
	meropenem[g]	Mpm
	amikacin *OR*	Am
	streptomycin[h]	(S)
	ethionamide *OR*	Eto
	prothionamide[i]	Pto
	p-aminosalicylic acid[i]	PAS

DST: drug-susceptibility testing; ECG: electrocardiogram; GDG: Guideline Development Group; IPD: individual patient data; LPA: line probe assay; MA: meta-analysis; MDR: multidrug-resistant; TB: tuberculosis.

[a] This table is intended to guide the design of individualized, longer MDR-TB regimens (the composition of the recommended shorter MDR-TB regimen is largely standardized; see Section 2). Medicines in Group C are ranked by decreasing order of usual preference for use subject to other considerations. The 2018 IPD-MA for longer regimens included no patients on thioacetazone and too few patients on gatifloxacin and high-dose isoniazid for a meaningful analysis. No recommendation on perchlozone, interferon gamma or sutezolid was possible owing to the absence of final patient treatment outcome data from appropriate studies (see Annex 5: https://www.who.int/publications/i/item/9789240007048).

[b] Bedaquiline is usually administered 400 mg orally once daily for the first two weeks, followed by 200 mg orally three times per week for 22 weeks (total duration of 24 weeks). Evidence on the safety and effectiveness of bedaquiline use beyond 6 months and below the age of 6 years was insufficient for review in 2018. Therefore, the use of bedaquiline beyond 6 months was implemented following best practices in "off-label" use. New evidence on the safety profile of bedaquiline use beyond 6 months was available to the GDG in 2019. Based on this evidence, the GDG were not able to assess the impact of prolonged bedaquiline use on efficacy, due to the limited evidence and potential residual confounding in the data. However, the evidence supports the safe use of bedaquiline beyond six months in patients who receive appropriate schedules of baseline and follow up monitoring. It is important to note that the use of bedaquline beyond six months still remains as off-label use and in this regard best practices in off-label use still apply.

c Evidence on the concurrent use of bedaquiline and delamanid was insufficient for review in 2018. In 2019, new evidence on the concurrent use of bedaquiline and delamanid was made available to the GDG. With regards to safety, the GDG concluded that the data suggest no additional safety concerns with regards to concurrent use of bedaquiline and delamanid. Both medicines may be used concurrently among patients who have limited other treatment options available to them, and if sufficient monitoring (including baseline and follow up ECG and electrolyte monitoring) is in place. The data on the effectiveness of concurrent use of bedaquiline and delamanid were reviewed by the GDG, but due to the limited evidence and potential residual confounding in the data, the GDG were unable to proceed with a recommendation on effectiveness.

[d] Use of linezolid for at least 6 months was shown to increase effectiveness, although toxicity may limit use. The analysis suggested that using linezolid for the whole duration of treatment would optimize its effect (about 70% of patients on linezolid with data received it for more than 6 months and 30% for 18 months or the whole duration). No patient predictors for early cessation of linezolid could be inferred from the IPD sub-analysis.

[e] Evidence on the safety and effectiveness of delamanid beyond 6 months and below the age of 3 years was insufficient for review. Use of delamanid beyond these limits should follow best practices in "off-label" use.

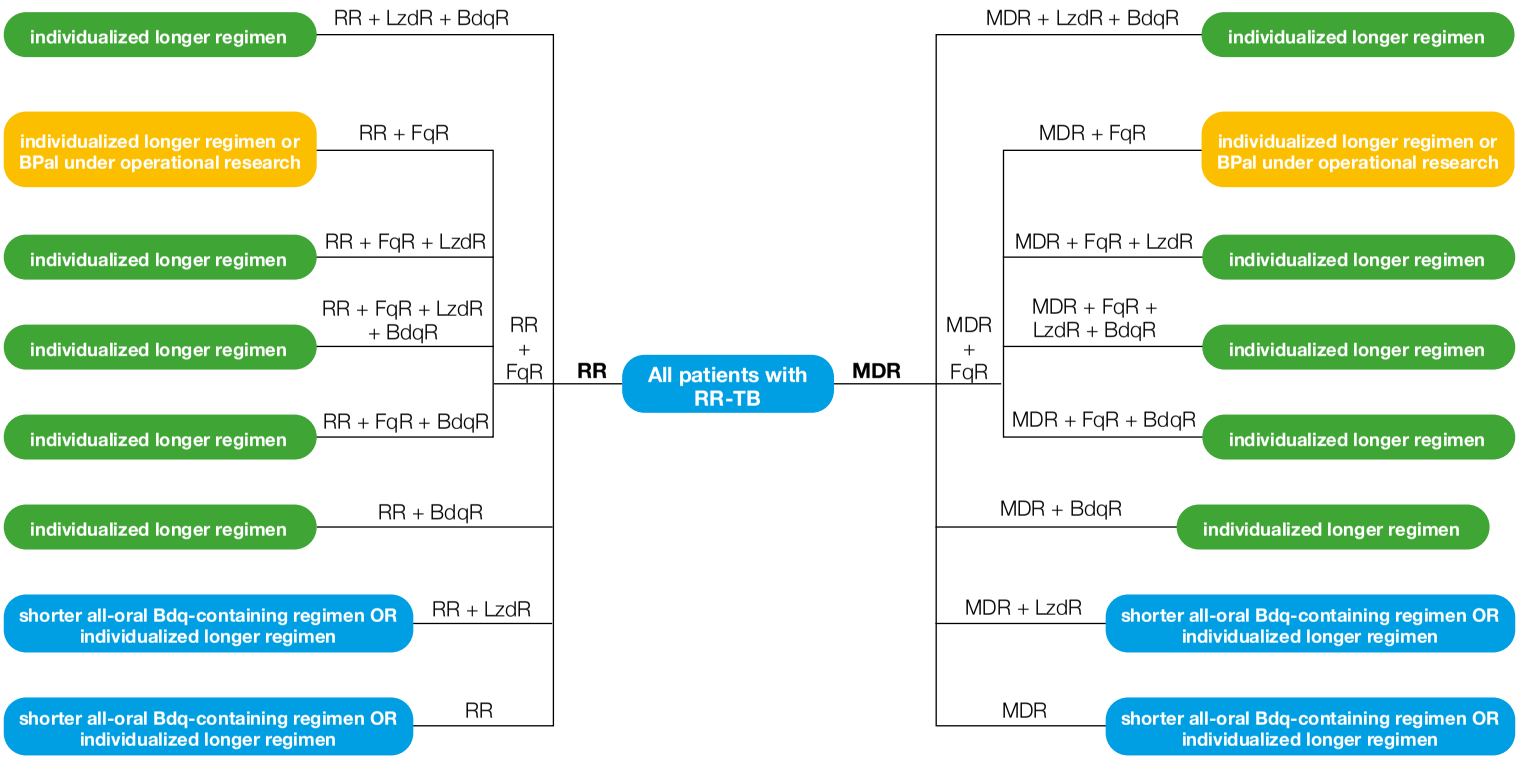
[f] Pyrazinamide is counted as an effective agent only when DST results confirm susceptibility.

[g] Every dose of imipenem–cilastatin and meropenem is administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.

[h] Amikacin and streptomycin are to be considered only if DST results confirm susceptibility and high-quality audiometry monitoring for hearing loss can be ensured. Streptomycin is to be considered only if amikacin cannot be used (unavailable or documented resistance) and if DST results confirm susceptibility (resistance to streptomycin is not detectable with second-line molecular LPAs and phenotypic DST is required). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.

[i] These agents showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are thus proposed only when other options to compose a regimen are not possible.

Annex 2: Possible resistance patterns to second-line drugs in Group A and related treatment regimen options



Bdq: bedaquiline; BdqR: resistant to bedaquiline; BPaL: bedaquiline, pretomanid and linezolid; FqR: resistant to a fluoroquinolone; LzdR: resistant to linezolid; MDR: multidrug-resistant; RR: rifampicin resistant; TB: tuberculosis.

Annex 3: Possible revised definitions of XDR-TB and their potential advantages, disadvantages and implications

	Revised XDR-TB definition	Advantages	Disadvantages	Implications
1	Fluoroquinolone resistant TB in addition to MDR/RR-TB	• Rapid DST for resistance to fluoroquinolones is available • Resistance to fluoroquinolones leads to important clinical decisions between regimen options • Effective treatment options are available, either individualized longer regimens or BPaL under operational research conditions • It may be easier for national TB programme surveillance systems to adapt to this definition because it is already used	• It may not capture the sickest patients or those with very extensive drug resistance profiles • The extent of bedaquiline or linezolid resistance (or resistance to any other SL drugs) may not be seen as important, and in the future it will probably be very important to monitor for resistance to these medicines	• The definition does not indicate a major drop in treatment effectiveness since effective treatment options are available for patients with fluoroquinolone-resistant TB • Testing for fluoroquinolone resistance has a clear clinical benefit and there will be a clear group of patients who cannot benefit from the shorter regimen • NTPs will need to test for fluoroquinolone resistance to determine eligibility for the shorter (or longer) regimen; therefore, resource use may not be a major issue
2	Fluoroquinolone and bedaquiline resistant TB in addition to MDR/RR-TB	• Effective treatment options are available using only individualized longer regimens • Rapid DST for resistance to fluoroquinolones is available • DST for resistance to bedaquiline is likely to become increasingly necessary as both shorter and longer regimens and the BPaL regimen feature bedaquiline; therefore, it will become important for clinical and surveillance purposes and to protect bedaquiline as a key SL drug	• Only phenotypic DST for resistance to bedaquiline is available and it is not widely used • It may initially take time to adapt national TB surveillance systems to accommodate this change	• Effective treatment options are available using individualized longer regimens • Clinical decisions based on pDST can take several weeks or months, meaning that empiric treatment is used while waiting for results • The availability of bedaquiline DST enables clear identification of patients who cannot benefit from the shorter regimen • This will require additional resources (and time) to scale up in laboratories and programmes, but it will have long-term benefits

	Revised XDR-TB definition	Advantages	Disadvantages	Implications
3	Fluoroquinolone and linezolid resistant TB in addition to MDR/RR-TB	• Effective treatment options are available using only individualized longer regimens • Rapid DST for fluoroquinolones is available • DST for resistance to linezolid is likely to become increasingly necessary as the longer regimens and the BPaL regimen feature linezolid; therefore, it will become important for clinical and surveillance purposes and to protect linezolid as a key SL drug	• Only pDST for resistance to linezolid is available and it is not widely used • It may initially take time to adapt national TB surveillance systems to accommodate this change	• Effective treatment options are available using individualized longer regimens • Clinical decisions based on pDST can take several weeks or months, meaning that empiric treatment is used while waiting for results • The availability of linezolid DST enables clear identification of patients who cannot benefit from the shorter regimen or the BPaL regimen • This will require additional resources (and time) to scale up in laboratories and programmes, but it will have long-term benefits
4	Fluoroquinolone, bedaquiline and linezolid resistant TB in addition to MDR/RR-TB	• Rapid DST for resistance to fluoroquinolones is available • These patients are likely to have very poor treatment outcomes, and designing effective regimens for these patients will rely on knowing the DST profile	• Less effective treatment options are available using individualized longer regimens only • Only pDST for resistance to bedaquiline is available and it is not currently widely used • Only pDST for resistance to linezolid is available and it is not currently widely used • It may initially take time to adapt national TB surveillance systems to accommodate this change	• Clinical decisions based on pDST can take several weeks or months, meaning that empiric treatment is used while waiting for results • The availability of bedaquiline and/or linezolid DST enables clear identification of patients who cannot benefit from the shorter regimen or the BPaL regimen • The availability of bedaquiline and/or linezolid DST makes it possible to identify patients who have less effective treatment options with Group B and C drugs using an individualized longer regimen • This will require additional resources (and time) to scale up in laboratories and programmes, but it will have long-term benefits
5	Resistance to any two Group A drugs in addition to MDR/RR-TB	• May differ from the advantages given above, depending on which Group A drugs resistance is identified	• May differ from the advantages given above, depending on which Group A drugs resistance is identified	• May differ from the advantages given above, depending on which Group A drugs resistance is identified

BPaL: bedaquiline, pretomanid and linezolid; DST: drug-susceptibility testing; MDR/RR-TB: multidrug- or rifampicin-resistant tuberculosis; pDST: phenotypic drug susceptibility testing; SL: second line; TB: tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

Annex 4: Algorithm for longer MDR-TB regimen composition in commonplace situations of resistance pattern or contraindication[a]

Medicines to which there is resistance or contraindication of use		Consider adding medicines likely or confirmed to be effective			Examples of regimens
		Group A	Group B	Group C[b]	
1	None of the Group A or B medicines[c]	All 3 medicines	1 medicine	Not usually needed	18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-Lzd-(Cfz or Cs)
2	One Group A medicine	Remaining 2 medicines	Both medicines	May be needed	18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-Cfz-Cs 18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-Cfz-Cs-($Dlm_{(6\ m\ or\ longer)}$ or Z or E)
					18 (Lfx or Mfx)-Lzd-Cfz-Cs 18 (Lfx or Mfx)-Lzd-Cfz-Cs-($Dlm_{(6\ m\ or\ longer)}$ or Z or E)
					18 $Bdq_{(6\ m\ or\ longer)}$-Lzd-Cfz-Cs 18 $Bdq_{(6\ m\ or\ longer)}$-Lzd-Cfz-Cs-($Dlm_{(6\ m\ or\ longer)}$ or Z or E) If there is a suspected resistance to E or Z, replace with Group C drugs
3	Two Group A medicines	Remaining medicine	Both medicines	At least 1 medicine	18 $Bdq_{(6\ m\ or\ longer)}$-Cfz-Cs-$Dlm_{(6\ m\ or\ longer)}$-(Z or E) 18 Lzd-Cfz-Cs-$Dlm_{(6\ m\ or\ longer)}$-(Z or E) 18 Lfx-Cfz-Cs-$Dlm_{(6\ m\ or\ longer)}$-(Z or E) If there is a suspected resistance to E or Z, replace with Group C drugs
4	One Group B medicine	All 3 medicines	Remaining medicine	May not be needed	18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-Lzd-(Cfz or Cs)
5	Both Group B medicines	All 3 medicines	None	1 or 2 medicines	18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-Lzd – $Dlm_{(6\ m\ or\ longer)}$-(Z or E) If there is a suspected resistance to E or Z, replace with Group C drugs

Medicines to which there is resistance or contraindication of use		Consider adding medicines likely or confirmed to be effective			Examples of regimens
		Group A	Group B	Group C[b]	
6	One Group A and both Group B medicines	Remaining 2 medicines	None	At least 3 medicines	18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-$Dlm_{(6\ m\ or\ longer)}$-Z-E
					18 (Lfx or Mfx)-Lzd-$Dlm_{(6\ m\ or\ longer)}$-Z-E
					18 $Bdq_{(6\ m\ or\ longer)}$-Lzd-$Dlm_{(6\ m\ or\ longer)}$-Z-E If there is a suspected resistance to E or Z, replace with Group C drugs
7	All Group A medicines	None[d]	Both	3 or more medicines	18–20 Cfz-Cs-Dlm-Z-E or other combinations of Group C drugs depending on known or suspected resistance

Bdq: bedaquiline; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; E: ethambutol; Lfx: linezolid; m: months; MDR-TB: multidrug-resistant tuberculosis; MDR/RR-TB: multidrug- or rifampicin-resistant tuberculosis; Mfx: moxifloxacin; MIC: minimum inhibitory concentration; TB: tuberculosis; WHO: World Health Organization; Z: pyrazinamide.

[a] Situations shown are not exhaustive. Other factors may influence choice, such as patient risk for poor outcome or drug–drug interactions, clinician and patient preference and availability of a medicine. More medicines than the recommended minimum may be added if there is limited confidence in the effectiveness of regimen components, if the patient was exposed in a setting where second-line TB drug resistance is frequent and longer MDR-TB regimens perform poorly despite good programmatic management of MDR/RR-TB. For MDR-TB with confirmed fluoroquinolone resistance, no fluoroquinolone is used, and if Group C agents are needed the recommended WHO grouping will be followed based on benefit versus risk and individual circumstances.

[b] The choice and number of Group C medicines to include depends on the confidence in the effectiveness of medicines in this group and the other components of the regimen; thus: if four Group A and B agents are included and there is confidence in all of them, then Group C agents are not needed; if three Group A and B agents are included and there is confidence in all of them, then at least one Group C agent is added; and if two Group A and B agents are included and there is confidence in all of them, then at least three Group C agents are added.

[c] Regardless of resistance or contraindication for Group C medicines.

[d] Moxifloxacin, a later generation fluoroquinolone, may still be effective at high dose when the fluoroquinolone MIC is below the clinical breakpoint. If the MIC is elevated, then fluoroquinolones are not used, and additional Group C agents will be needed.

Annex 5: Agenda for the expert consultation meeting on the definition of XDR-TB

Tuesday 27 October 2020		
Time (CET)	**Topic**	**Speaker / Chair**
14:00–14:15	Welcome and opening statements	Tereza Kasaeva, Director Global TB Programme, WHO
14:15–14:45	Introduction and meeting objectives WHO recommendations on treatment of drug-resistant TB and future outlook	Fuad Mirzayev Global TB Programme, WHO
14:45–15:05	WHO recommendations on TB diagnostics and TB diagnostics pipeline	Nazir Ismail Global TB Programme, WHO
15:05–15:20	TB drug resistance surveys	Anna Dean Global TB Programme, WHO
15:20–15:40	Questions and discussion	Fuad Mirzayev Global TB Programme, WHO
15:40–15:50	Short break	
15:50–16:10	Treatment outcomes for patients with drug-resistant TB	Maroussia Roelens University of Geneva
16:10–17:00	Questions and discussion, including on principles that would underlie a change in the definition of XDR-TB	Fuad Mirzayev Global TB Programme, WHO
Wednesday 28 October 2020		
Time (CET)	**Topic**	**Speaker / Chair**
14:00–15:30	Moderated discussion on the principles underlying a change in the definition of XDR-TB	Mario Raviglione University of Milan
15:30–15:40	Short break	
15:40–17:00	Discussion on the definition of XDR-TB	Mario Raviglione University of Milan
Thursday 29 October 2020		
Time (CET)	**Topic**	**Speaker / Chair**
14:00–14:15	Brief recap of where we are at, including revision of principles	Matteo Zignol Global TB Programme, WHO
14:15–15:30	Discussion on options for the definition of XDR-TB	Jeremiah Chakaya NTP Kenya
15:30–15:40	Short break	
15:40–16:45	Discussion on options for the definition of XDR-TB	Jeremiah Chakaya NTP Kenya
16:45–17:00	Summary of the definition of XDR-TB and next steps	Matteo Zignol Global TB Programme, WHO

CET: Central European Time; NTP: national tuberculosis programme; TB: tuberculosis; WHO: World Health Organization; XDR-TB: extensively drug-resistant tuberculosis.

Annex 6: List of participants for the expert consultation meeting on the definition of XDR-TB

No.	Name	Organization	Country
1	Charles Daley	National Jewish Health, Denver	United States of America
2	Anneke Hesseling	Stellenbosch University	South Africa
3	Carole Mitnick	Harvard University	United States of America
4	Zarir Udwadia	Hinduja Hospital and Medical Research Centre, Mumbai	India
5	Christoph Lange	German Center for Infection Research, Borstel	Germany
6	Giovanni Battista Migliori	WHO Collaborating Centre for TB and Lung Diseases, Maugeri Institute, Tradate	Italy
7	Mario Raviglione	University of Milan	Italy
8	Olivia Keiser	Institute of Global Health, University of Geneva	Switzerland
9	Janne Estill	Institute of Global Health, University of Geneva	Switzerland
10	Simon Tiberi	Barts Health, NHS	United Kingdom of Great Britain and Northern Ireland
11	Francesca Conradie	University of Witwatersrand	South Africa
12	Keertan Dheda	University of Cape Town	South Africa
13	Jonathon Campbell	McGill University, Montreal	Canada
14	Norbert Ndjeka	Government of South Africa	South Africa
15	Irina Vasilyeva	Government of the Russian Federation	Russian Federation
16	Yuhong Liu	Government of China	China
17	Kuldeep Sachdeva	Government of India	India
18	Julia Rios	Government of Peru	Peru
19	Tutik Kusmiati	Airlangga University, Dr Soetomo Hospital	Indonesia
20	Alena Skrahina	Government of Belarus	Belarus
21	Thandar Hmun	Government of Myanmar Aung San TB Hospital	Myanmar
22	Lucica Ditiu	Stop TB Partnership	Switzerland

No.	Name	Organization	Country
23	Morten Ruhwald	FIND	Switzerland
24	Cathy Hewison	Médecins sans Frontières	France
25	Agnes Gebhard	KNCV	Netherlands
26	Kobto Koura	The International Union Against TB and Lung Disease	France
27	Draurio Barreira	UNITAID	Switzerland
28	Mohammed Yassin	Global Fund to Fight AIDS, Tuberculosis and Malaria	Switzerland
29	Marlena Kaczmarek	European Centre for Disease Prevention and Control	Sweden
30	Mukadi Ya Diul	United States Agency for International Development	United States of America
31	Charles Wells	Bill & Melinda Gates Foundation (Medical Research Institute)	United States of America
32	Mel Spigelman	TB Alliance	United States of America
33	Daniela Cirillo	TB Supranational Reference Laboratory (SRL) Milan	Italy
34	Harald Hoffmann	SRL Gauting	Germany
35	Dissou Affolabi	SRL Cotonou	Benin
36	Moses Joloba	SRL Kampala	Uganda
37	Rumina Hassan	SRL Pakistan	Pakistan
38	Vithal Prasad Myneedu	National Reference Laboratory (NRL)	India
39	Renzong Li	NRL	China
40	Diana Vakhrusheva	NRL	Russian Federation
41	Lindsay McKenna	Treatment Action Group	United States of America
42	Jamilya Ismoilova	Civil Society Taskforce	Tajikistan
43	Angela Starks	Centers for Disease Control and Prevention	United States of America
44	Heather Alexander	Centers for Disease Control and Prevention	United States of America
45	Sarabjit Chadha	Global Drug-resistant TB Initiative	India
46	Jeremiah Chakaya Muhwa	Technical expert, national tuberculosis programme (NTP) Kenya	Kenya

No.	Name	Who staff	Country
47	Tauhid Islam	WHO Regional Office for the Western Pacific (WPRO)	Philippines
48	Mukta Sharma	WHO Regional Office for South-East Asia (SEARO)	India
49	Vineet Bhatia	WHO SEARO	India
50	Askar Yedilbayev	WHO Regional Office for Europe	Denmark
51	Rafael Lopez Olarte	WHO Regional Office for the Americas	United States of America
52	Muhammad Akhtar	WHO Regional Office for the Eastern Mediterranean	Egypt
53	Jean Louis Abena Foe	WHO Regional Office for Africa (AFRO)	Congo
54	Michel Gasana	WHO AFRO	Congo
55	Tereza Kasaeva	WHO Global TB Programme	Switzerland
56	Matteo Zignol	WHO Global TB Programme	Switzerland
57	Fuad Mirzayev	WHO Global TB Programme	Switzerland
58	Medea Gegia	WHO Global TB Programme	Switzerland
59	Linh Nguyen	WHO Global TB Programme	Switzerland
60	Kerri Viney	WHO Global TB Programme	Switzerland
61	Dennis Falzon	WHO Global TB Programme	Switzerland
62	Ernesto Jaramillo	WHO Global TB Programme	Switzerland
63	Nazir Ismail	WHO Global TB Programme	Switzerland
64	Philippe Glaziou	WHO Global TB Programme	Switzerland
65	Anna Dean	WHO Global TB Programme	Switzerland
66	Marek Lalli	WHO Global TB Programme	Switzerland
67	Marie-Christine Bartens	WHO Global TB Programme	Switzerland
68	Nick Argent	WHO Pre-qualification programme	Switzerland
69	Kitty van Weezenbeek	WHO Antimicrobial Resistance/ Surveillance, Prevention and Control (AMR/SPC)	Switzerland
70	Olga Tosas Auguet	WHO Global TB Programme	Switzerland
71	Kyung Hyun Oh	WHO WPRO	Philippines

Global TB Programme
World Health Organization
Avenue Appia 20, CH-1211
Geneva-27, Switzerland

9789240018662