Impact of the revised definition of extensively drug resistant tuberculosis

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Ethics Approval and Consent to Participate:

According to French regulation at the time of start of the study and in accordance with the ethical standards of our hospitals' institutional review boards (Committee for the Protection of Human Subjects), informed consent was not sought because this observational study did not modify existing diagnostic or therapeutic strategies, and is focused on strains' drug susceptibility without collection of patients' data.

Recently, the World Health Organization (WHO) has released a revised definition of extensively drug-resistant tuberculosis (XDR-TB) that should be used for clinical and surveillance purposes starting from January 1st, 2021 [1, 2]. The previous definition of XDR-TB TB was TB that is resistant to any fluoroquinolone (levofloxacin and/or moxifloxacin) and to at least one of three second-line injectable drugs (SLI, capreomycin, kanamycin and amikacin), in addition to multidrug resistance. The revised definition is: TB caused by *Mycobacterium tuberculosis* strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug. WHO Group A drugs currently include fluoroquinolones (levofloxacin or moxifloxacin), linezolid and bedaquiline. In addition, pre-XDR-TB is now a WHO-endorsed definition, identified as MDR/RR-TB with any fluoroquinolone resistance. Although the previous definition of XDR-TB has proved to be predictive of poor treatment outcome [3], the 2020 update appears in line with recent changes of treatment regimens given i.e. less frequent use of SLI in favor of potent oral drugs bedaquiline and linezolid. Moreover, a large meta-analysis failed to show an association between mortality reduction and SLI use whereas this association was shown for bedaquiline and linezolid [4]. In this study, we aimed to measure retrospectively the impact of the revised definition on the epidemiology of XDR-TB in France.

The French National Reference Centre of Mycobacteria (CNR-MyRMA, Paris, France) receives the MDR-TB strains of each new MDR-TB case identified in France and performs complete phenotypic drug susceptibility testing (DST) using the proportion method. Linezolid (1 mg/L) and ofloxacin (2 mg/L formerly, currently transitioning to moxifloxacin following WHO recommendations) are tested in Lowenstein-Jensen and bedaquiline (0.25 mg/L) is routinely tested in 7H11. CNR-MyRMA has received certification for second-line proficiency testing by the European Reference Laboratory Network for TB (ERLTB-Net) during this period. We retrospectively re-analyzed phenotypic DST results of all MDR-TB strains received by CNR-MyRMA between January 1st, 2017 and December 31st, 2020. Anonymized data were retrieved from the CNR-MyRMA database. Rates of drug-resistant strains according to old and revised definitions were calculated, and 95% confidence intervals were provided. Data analysis was performed using Stata software version 15.0 (StataCorp).

Overall, the total number of XDR strains over these four years was 37 according to the old definition compared to six with the revised definition (table). As a consequence, the percentage of XDR strains among all MDR strains decreased from 12.6% (95% CI 9.0-16.9) according to the old definition to 2.0% (95% CI 0.7-4.4) according to the revised definition. All six strains classified XDR according to the revised definition were also classified XDR according to the old definition. Overall, in the same period, 57 strains (19.4%, 95% CI 15.0-24.4) with resistance to any fluoroquinolone were identified. Among these, 51 strains (17.4%, 95% CI 13.2-22.2) would be classified as pre-XDR-TB according to the revised definition. Among the six XDR strains identified according to the revised definition, two were resistant to both linezolid and bedaquiline, i.e. resistant to all three WHO Group A drugs, representing as such the most difficult to treat cases with currently available drugs. Interestingly, among strains resistant to either bedaquiline, linezolid, or both, the majority (6/8) were also fluoroquinolone-resistant (and thus classified as XDR). Overall, the low percentage of MDR strains with additional resistance to bedaquiline and/or linezolid in France is reassuring.

According to the results of our study, the revised definition will dramatically reduce the number of cases of TB classified as XDR in France. It will likely be also the case in many other countries in western Europe. One possible limit of the revised definition is represented by technical challenges and limited availability of DST capacity worldwide for detection of bedaquiline and linezolid resistance. The phenotypic DST is performed at the CNR-MyRMA with in-house prepared media requiring a high workload and skilled technicians. An alternative is a recently developed 14-Drug microtiter plate containing both bedaquiline and linezolid [5]. However, this will still require BSL-3 containment. To the best of our knowledge, the only currently available commercial genotypic tests is Deeplex®, a deep-sequencing technique which allows detection of bedaquiline (only *rv0678*) and linezolid resistance [6]. Thus, even in areas where MDR-TB strains with linezolid and bedaquiline resistance are more frequent, such strains may not be detected due to lack of DST availability. National programs should urgently implement DST for bedaquiline and linezolid in order to avoid a false disappearance of XDR-TB. Additionally, in France, XDR strains handling is subject to specific authorizations from a National agency (ANSM): the

revised definition would reduce by 80% the number of strains that have been concerned by this regulation since 2017.

In our study, all the strains classified as XDR according to the revised definition were also classified as XDR according to the old definition. This finding confirms that the revised definition focuses on the subset of the previous XDR cases that includes the most difficult to treat patients.

In 2020, WHO has released an update on the treatment of drug-resistant TB [7]. According to this document the Nix-TB regimen, including bedaquiline, pretomanid, and linezolid, may be used for XDR-TB under operational research conditions [8]. Given the multiple reports on the rising frequency of primary bedaquiline resistance [9], national programs should, as mentioned in the report, be clearly encouraged to screen for bedaquiline resistance and not only rely on lack of previous bedaquiline treatment. We suggest that inclusion criteria for such operational research, includes baseline DST for all 3 drugs of the BPaL regimen.

In conclusion, the revised definition reduces the number of cases classified as XDR in France and will likely allow to better focus on the most relevant TB cases that deserve reporting and surveillance, i.e. on the most difficult to treat cases of TB. National programs should urgently implement DST for bedaquiline and linezolid. In the meantime, fluoroquinolone resistance, which can be detected by rapid genotypic tests endorsed by the WHO, should be used to detect pre-XDR-TB and to guide therapeutic decisions by clinicians [10].

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Table: number of *M. tuberculosis* strains classified as multidrug-resistant (MDR), MDR with additional fluoroquinolone resistance (MDR, FQ-R), and extensively drug-resistant (XDR) according to old and revised definitions, in France between 2017 and 2020.

	2017	**2018**	**2019**	**2020**	**Total**,% (95% CI)
MDR	**79**	**80**	**69**	**66**	**294**
MDR, FQ-S BDQ-S and LNZ-S	78	79	69	66	
MDR, FQ-S BDQ-R and LNZ-S	0	0	0	0	0
MDR, FQ-S BDQ-S and LNZ-R	1	1	0	0	2
MDR, FQ-S BDQ-R and LNZ-R	0	0	0	0	0
MDR, FQ-R* (%)	**14 (**17.7%)	**20** (25%)	**13** (18.8%)	**10** (14.5%)	**57**,19.4% (15.0-24.4)
XDR, old definition (%)	**10** (12.6%)	**11** (13.8%)	**10** (14.5%)	**6** (9.1%)	**37**, 12.6% (9.0-16.9)
XDR, revised definition (%)	**3 (**3.8%)	**2** (2.5%)	**1** (1.5%)	**0** (0%)	**6**, 2.0% (0.7-4.4)
XDR, revised definition BDQ-R and LNZ-S	1	1	0	0	2
XDR, revised definition BDQ-S and LNZ-R	1	0	1	0	2
XDR, revised definition BDQ-R and LNZ-R	1	1	0	0	2

CI = confidence interval, *pre-XDR-TB according to revised WHO definition