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Editorial: Updates from the World Health Organization (WHO) on Global Treatment Recommendations for Drug-Susceptible and Multidrug-Resistant Tuberculosis

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Abstract The World Health Organization (WHO) estimated that in 2019, 10.0 million people worldwide developed tuberculosis (TB), with 1.4 million deaths from TB in that year. Infection with *Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampin and an additional chemotherapeutic agent is known as multidrug-resistant TB (MDR TB). Until recently, the prevalence of drug resistance in patients with TB has been poorly understood due to a lack of infection surveillance and molecular testing. Countries with the highest prevalence of TB, including MDR TB, are also those most affected by the COVID-19 pandemic. The identification of MDR TB requires careful monitoring and resources for molecular testing. Previous treatment regimens have required intravenous treatments of long duration and high cost. The 2020 and 2021 recommendations from the WHO for the management of drug-susceptible TB and MDR TB have included oral treatment regimens and reduced treatment duration. This Editorial aims to present the rationale for the 2020 and 2021 recommendations from the WHO for the management of drug-susceptible TB and MDR TB.

Keywords: **Editorial • Tuberculosis • COVID-19 • Drug Resistance**

The genus, *Mycobacterium* is now believed to be millions of years old [1]. *Mycobacterium tuberculosis* (*M. tuberculosis*) may have infected humans since 2,400 BC, as vertebral deformities typical of Pott's disease, or spinal tuberculosis (TB), have been identified in preserved Egyptian mummies [1,2]. Cases of TB continue to rise due to the ability of *M. tuberculosis* to adapt and develop opportunistic infection strategies [3,4]. Recent pathogenic strategies include co-infection with the human immunodeficiency virus (HIV), which results in HIV-associated TB, and the development of strains that are resistant to multiple anti-TB therapies, or multidrug-resistant TB (MDR TB) [3,4].

Until recently, the prevalence of drug resistance in patients with TB has been poorly understood due to a lack of infection surveillance and molecular testing [3,4]. Infection with *M. tuberculosis* that is resistant to at least isoniazid and rifampin and an additional chemotherapeutic agent is known as MDR TB [3]. Infection with *M. tuberculosis* resistant to isoniazid, rifampin, and fluoroquinolones (levofloxacin or moxifloxacin) is now known as 'pre-extensively drug-resistant TB' (pre-XDR TB) [3,4]. Infection with *M. tuberculosis* resistant to at least isoniazid, rifampin, and any fluoroquinolone, and at least one additional group A drug, which currently includes bedaquiline and linezolid, is now known as 'extensively drug-resistant TB' (XDR TB) [3]. Totally drug-resistant TB (TDR TB) is an infection with *M. tuberculosis* resistant to all current medications [3,4].

Since 1997, the World Health Organization (WHO) has published an annual Global TB Report. The latest WHO Global TB report was published in October 2020 [5]. The WHO has estimated that in 2019, 10.0 million people worldwide developed active TB, with 1.4 million deaths due to TB in that year [5]. In 2019, the regions with the highest prevalence of TB were Africa (25%), South-East Asia (44%), and the Western Pacific (18%) region [5]. In 2019, eight countries and regions accounted for two-thirds of the global cases of TB, including China (8.4%), India (26%), Pakistan (5.7%), Nigeria (4.4%), Indonesia (8.5%), the Philippines (6.0%), South Africa (3.6%), and Bangladesh (3.6%) [5]. Also, in 2019 there were an additional 208,000 deaths in people with TB who were also HIV-positive [5]. In 2019, the main risk factors for TB were identified by the WHO as poverty, poor nutrition, diabetes, tobacco smoking, and air pollution [5]. The 2020 WHO report included a preliminary assessment of how the COVID-19 pandemic could affect the prevention and management of TB [5]. However, global efforts to control TB were not on track even before the COVID-19 pandemic. Diagnosis and treatment targets set by the United Nations (UN) in 2018 at the UN General Assembly

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meeting on TB, which was held in New York, USA, were not achieved by early 2020 [5,6].

Until recently, precise information about the global incidence of MDR TB has been difficult to obtain, as routine sputum culture and drug susceptibility testing are not performed routinely in all resource-limited settings, where the infection occurs most frequently [7]. Currently, the WHO collects data on MDR TB from more than 160 countries [5]. The latest WHO Global TB Report estimated that in 2019, there were 500,000 cases of MDR-TB worldwide [5]. However, in 2019, only 186,772 cases of MDR-TB were confirmed by laboratory and molecular investigations, and only 57% had positive treatment outcomes [5]. In the most recent report, the WHO highlighted the need for a more rapid and accurate diagnosis of MDR TB, screening for MDR TB, and improving treatment and patient follow-up [5]. Data collection has been improved by implementing infection surveillance supported by molecular testing [5]. Continuous monitoring of the prevalence of MDR TB may now be possible, even in countries with a high infection rate [5].

The treatment of patients with MDR TB and XDR TB has been challenging because of prolonged treatment duration of up to 24 months, drug toxicity, treatment cost, and poor clinical outcomes [8]. After four decades of lack of drug development, three new drugs, bedaquiline, delamanid, and pretomanid, were approved for the management of patients with MDR TB and XDR TB and were also endorsed by the WHO, with the possibility of shorter treatment duration [5,8]. In 2019, the American Thoracic Society (ATS), the US Centers for Disease Control and Prevention (CDC), the European Respiratory Society (ERS), and the Infectious Diseases Society of America (IDSA) sponsored new clinical guidelines for the treatment of MDR TB [9]. These guidelines were evidence-based from a review of published systematic reviews and meta-analysis data [9]. The study group recommended the most effective oral drug regimen for treating MDR TB, the role of surgery in treating MDR-TB, treatment of patient contacts, and treatment of isoniazid-resistant TB [9].

Since early 2020, the COVID-19 pandemic has had a direct and indirect detrimental impact on health services in all areas, including infectious diseases and TB services [10]. Prioritized health services, clinical studies, and vaccine and drug development to treat SARS-CoV-2 infection have diverted these applications and resources from other infectious diseases [10]. These effects of the COVID-19 pandemic have come when TB cases, combined infections with TB, and MDR TB have all been increasing globally [10]. It has recently been estimated that MDR-TB cases will rise in 2021 and 2022, further affecting already poor treatment outcomes [10]. There is an urgent need for continued drug development and the use of shorter treatment regimens for patients with MDR TB [5,10].

In November 2019, an independent international WHO expert panel reviewed new evidence on the treatment of MDR TB and rifampicin-resistant TB, and published new guidelines in June 2020 [11]. The WHO recommends a shorter treatment regimen of between 9 to 11 months for patients with MDR TB not resistant to fluoroquinolones, including oral bedaquiline [11,12]. For patients with MDR-TB who also have fluoroquinolone resistance, a regimen composed of bedaquiline, pretomanid, and linezolid may be used for between 6 to 9 months [11,12]. The oral drug treatment regimens may be individualized based on the severity of TB and the MDR TB molecular profile [11,12]. The data review from 2019 showed no safety concerns for the use of bedaquiline for more than 6 months' duration, the use of delamanid combined with bedaquiline, or the use of bedaquiline during pregnancy [11,12]. The WHO 2020 revised guidelines have highlighted the ongoing need for high-quality evidence from clinical trials to develop treatment guidelines [11].

On 14th June 2021, the WHO issued a rapid communication on the management of drug-susceptible TB, following a review of the evidence and status of available treatment regimens and considering the effects of the current COVID-19 pandemic [13]. The WHO recommends a four-month regimen for drug-susceptible TB, with a shorter treatment regimen, oral dosing, and has evaluated the safety and efficacy of the recommended regimen [13]. In support of these recommendations, in May 2021, the findings were published from an international phase 3 randomized, controlled trial funded partly by the US CDC (NCT02410772) [14]. The study compared patients with newly diagnosed TB treated with two four-month rifapentine-based regimens with a standard 6-month regimen [14]. The efficacy of a four-month rifapentine-based regimen containing moxifloxacin was non-inferior to the standard six-month regimen in the treatment of TB [14].

The shorter treatment regimens for both MDR TB and drug-susceptible TB, recently recommended by the WHO, would ease the burden on patients and healthcare systems, particularly during the COVID-19 pandemic [11,13]. The reduced duration of treatment may improve treatment compliance and reduce healthcare costs [11,13]. Implementing the new first-line WHO regimen for drug-susceptible TB would be facilitated by improved availability and reduced cost of rifapentine [13]. Also, patient monitoring will be required, as this regimen contains moxifloxacin, an antibiotic usually used to treat MDR TB [14].

Conclusions

Countries with the highest prevalence of TB, including MDR TB, have also been most affected by the COVID-19 pandemic. The identification of MDR TB requires careful monitoring and resources for molecular testing. Also, previous treatment

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regimens have required intravenous treatments of long duration and high cost. The 2020 and 2021 recommendations from the WHO for the management of drug-susceptible TB and MDR TB have included oral treatment regimens and reduced treatment duration. Therefore, these clinical recommendations from the WHO will have a global impact, particularly in countries with a high and increasing incidence of drug-susceptible TB and MDR TB.

References:

1. Barberis I, Bragazzi NL, Galluzzo L, Martini M. The history of tuberculosis: From the first historical records to the isolation of Koch's bacillus. J Prev Med Hyg. 2017;58(1):E9-12
2. Morse D, Brothwell DR, Ucko PJ. Tuberculosis in ancient Egypt. Am Rev Respir Dis. 1964;90:524-41
3. Viney K, Linh NN, Gegia M, et al. New definitions of pre-extensively and extensively drug-resistant tuberculosis: Update from the World Health Organization. Eur Respir J. 2021;57(4):2100361
4. Velayati AA, Masjedi MR, Farnia P, et al. Emergence of new forms of totally drug-resistant tuberculosis bacilli: Super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. Chest. 2009;136:420.
5. World Health Organization (WHO) 2020. Global Tuberculosis Report. Geneva. Available at: https://www.who.int/publications/i/item/9789240013131
6. United Nations General Assembly (UNGA). A/RES/73/3. Political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis. Available at: http://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/73/3
7. Zignol M, Dean AS, Falzon D, et al. Twenty years of global surveillance of antituberculosis drug resistance. N Engl J Med. 2016;375:1081
8. Pontali E, Raviglione MC, Migliori GB; and the Writing Group Members of the Global TB Network Clinical Trials Committee. Regimens to treat multidrug-resistant tuberculosis: past, present and future perspectives. Eur Respir Rev. 2019;28(152):190035
9. Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med. 2019;200(10):e93-142
10. Tiberi S, Vjecha MJ, Zumla A, et al. Accelerating development of new shorter TB treatment regimens in anticipation of a resurgence of multi-drug resistant TB due to the COVID-19 pandemic. Int J Infect Dis. 2021:S1201-9712(21)00153-3 [Online ahead of print]
11. World Health Organization (WHO). 2019. Consolidated guidelines on drug-resistant tuberculosis treatment. Geneva. Available at: https://www.ncbi.nlm.nih.gov/books/NBK539517/
12. Mirzayev F, Viney K, Linh NN, et al. World Health Organization recommendations on the treatment of drug-resistant tuberculosis, 2020 update. Eur Respir J. 2021;b57(6):2003300
13. World Health Organization (WHO). Treatment of drug-susceptible tuberculosis: Rapid communication. 14th June 2021. Available at: https://www.who.int/publications/i/item/9789240028678
14. Dorman SE, Nahid P, Kurbatova EV, et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. N Engl J Med. 2021;384(18):1705-18

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]