WHO recommendations on shorter treatment of multidrug-resistant tuberculosis

Tuberculosis is now the world's commonest cause of death from infectious disease.[1] The ominous spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis, and the scarce treatment options available, are priority global health issues.[2] With a global estimate in 2014 of 450 000 cases of MDR and XDR tuberculosis causing 150 000 deaths,[1] and the continuing spread, the WHO End TB Strategy[3] highlights the threat that MDR and XDR tuberculosis pose to global public health security. Poor treatment success of available treatment regimens and evolution of *Mycobacterium tuberculosis* strains with resistance patterns beyond XDR tuberculosis[4] pose major management challenges. Available treatment regimens have poor efficacy, are toxic and expensive, and require lengthy treatment, compromising patient adherence and therapeutic drug monitoring.[5] Furthermore, health-care providers find it difficult to design effective regimens because of inadequate laboratory facilities for tuberculosis drug susceptibility testing (DST).[6]

The recent release by WHO of new recommendations aimed at speeding up tuberculosis DST using a rapid molecular MTBDRsl test and use of shorter MDR tuberculosis treatment regimens[7] is a welcome, long-awaited development. The recommendations highlight the advantages of the new regimen (4–6 months of kanamycin acid, moxifloxacin, protionamide, clofazimine, pyrazinamide and high-dose isoniazid and ethambutol followed by 5 months of moxifloxacin, clofazimine, pyrazinamide, and ethambutol), and provide a fact sheet with the necessary explanations. The shorter duration (9 months) and its low cost (<US$1000) will go some way in improving the current dismal status quo. The regimen is recommended only for MDR tuberculosis cases not previously treated with, or resistant to, second-line anti-tuberculosis drugs.

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Although the new guidelines are welcomed, we have concerns about whether the shorter treatment regimen is likely to be effective in all geographical settings. The WHO recommendations are based on a multicentre study of 1200 patients, not geographically representative of all MDR and XDR tuberculosis endemic regions, and they might not be applicable in specific hotspots for MDR and XDR tuberculosis, such as countries of the former Soviet Union in which there are numerous previously treated cases. Thus, a cautious decision-making approach, based on DST, is essential. However, the short regimens have produced excellent outcomes under operational research conditions in some settings[8–10] in which they benefited from pre-existing knowledge of the local epidemiology of drug resistance and availability of rapid MTBDRsl testing to ensure DST for the key drugs composing the treatment regimen. Under these conditions, the WHO-recommended short MDR tuberculosis regimen could be very useful for some patients, as treatment duration is substantially reduced.

Data show that the short regimen, previously called the Bangladesh regimen, might not be theoretically effective in certain settings. Our International Carbapenems Study Group recently did a multicentre, retrospective cohort study of 348 patients recruited in several clinical centres specialised in the management of MDR and XDR tuberculosis cases and located in eight countries in Europe and three countries in South America.[11,12] Adults with a culture-confirmed diagnosis of MDR tuberculosis were assessed according to meropenem-containing and imipenem-containing,

and meropenem-sparing and imipenem-sparing, regimens. The majority of the *M tuberculosis* strains that were isolated were resistant to one or more of the second-line drugs recommended by the WHO shorter regimen (resistance to kanamycin acid, 44·4%; quinolones, 40·8%; protionamide, 55·4%; pyrazinamide, 60·5%; and ethambutol, 68·4%); therefore, we estimate that the WHO regimen would have had a minimal impact in the selected group of patients in these settings. Prospective case-controlled studies are required to accurately assess the suitability of the shorter regimen in all regions in which MDR and XDR tuberculosis are endemic.

Another concern regarding the WHO-recommended shorter regimen is low availability of the rapid molecular MTBDRsl test and other laboratory facilities for DST in most MDR and XDR tuberculosis-endemic countries. Patients with MDR and XDR tuberculosis will invariably receive inappropriate therapy without these resources, which in turn can lead to selection of XDR strains of *M tuberculosis*. Furthermore, the treatment of MDR and XDR tuberculosis depends on the attending health-care worker or clinician tailoring the regimen according to the extent of the disease, its anatomical location, potential drug toxicities, patient psychological wellbeing, and likelihood of non-adherence to drug therapy. These are major challenges compounded by weaknesses in the national tuberculosis programmes of many low-income and middle-income countries, and high losses to follow-up due to the lengthy treatment. Notably, even if treatment is effective, a large proportion of people who survive have long-term functional disability, and are not able to return to full-time gainful work.[13] Any new tuberculosis drug regimen, including this short regimen promoted by WHO, needs to be coupled with a holistic approach to treating patients with MDR and XDR tuberculosis, tackling operational issues, government commitment to improvement of tuberculosis services, and investments into new innovations[14] that can be used as adjunct therapy to prevent lung damage and long-term disability.

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