Challenges in Controlling Multiple Drug-Resistant Tuberculosis in Endemic Settings

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January 13, 2010

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In 1993 the World Health Organization (WHO) introduced the Directly Observed Therapy Short course (DOTS) program, a multi-pronged approach including monitoring and treating of tuberculosis (TB) cases to combat the worldwide TB epidemic that was causing over 2 million deaths each year. While DOTS has decreased TB prevalence and death rates, global TB control is being increasingly challenged by the emergence of multiple drug-resistant (MDR)-TB [1]. WHO estimates that 511,000 MDR-TB cases occurred worldwide in 2007 alone,[2,3] yet currently the number of MDR-TB patients receiving treatment is less than 1-2% of the total number of TB cases – far below WHO annual targets[1,4]. Standard DOTS treatments are ineffective for treating patients with MDR strains[5]. Second-line drugs to treat MDR-TB are available, but these treatments are longer (minimum 18 months), are more toxic and can cost 100-fold more than first-line drugs alone[5,6,7]. Recognizing the threat MDR disease poses to TB control worldwide, WHO and Stop TB partnership introduced the DOTS-plus program in 2006, including a new target of treating 1.6 million cases of MDR-TB by 2015[1]. Whether the existing DOTS program or the more recently established DOTS-plus program will be sufficient to control MDR-TB however, remains uncertain.

While the DOTS-plus program provides a strategy for provision and completion of second-line drug treatments, there are additional pragmatic challenges to preventing the spread of MDR-TB. In order to optimize efficacy of current treatment regimens, a patient's previous treatment history or ideally, drug-susceptibility testing (DST) results are required[4,7]. DST is practical in most industrialized countries, but is not routinely available in many TB-endemic countries. Even in optimum settings, DST results may be available only several weeks after specimen collection. During this time, TB patients are often given empiric first-line treatment based on clinical suspicion and initial sputum tests prior to receiving MDR-TB resistance profiles. Consequently, many MDR-TB patients receive possibly ineffective treatment that may contribute to the progression of their disease and continued transmission of the drug-resistant strain. While new

rapid diagnostics for MDR-TB exist as research tools, presently there is no gold standard rapid MDR-TB diagnostic with widespread clinical acceptance[8,9]. New methods for accurately and rapidly diagnosing MDR-TB should greatly improve the ability to treat MDR-TB cases in a timely manner.

While earlier diagnosis of MDR-TB will require clinical and laboratory improvements, preventing ongoing spread of drug-resistant strains in the community also is a critical TB control concern. Primary MDR-TB (MDR disease in new TB patients with no history of previous treatment) now accounts for the majority of global MDR-TB cases[10]. Several studies have found that close contacts of MDR-TB patients have very high rates of MDR-TB[7, 11-15]. Knowledge that symptomatic patients have had close contact with an MDR-TB case may improve preferential DST and empiric treatments in settings where routine testing of all patients is not possible. At present contact tracing is recommended by WHO for all close contacts of MDR-TB cases; however, whether this practice actually occurs systematically in endemic countries is questionable due to limited resources and high case burden[7]. With MDR-TB, case detection needs to be actively shortened in order to improve delays in diagnosis and in order to reduce the length of the infectious period during which a case is likely to propagate the drug-resistant strain. While symptomatic cases usually present for care, given the heightened concern for MDR-TB transmission, actively seeking out high-risk persons who may have MDR-TB should be considered a priority. Venues such as prisons and hospitals also are hubs of MDR-TB transmission in some countries, and these settings may require targeted screening[7].

There is an urgent need for new and more effective treatment regimens for MDR-TB. However, even as new treatments become available the largest potential to improve MDR-TB treatment and control is early and accurate diagnosis of drug-resistance, which requires accurate rapid DST and strategic case finding. While rapid DST development and contact tracing often take secondary

priority to treatment development, these preventive measures are in fact integral to the success of MDR-TB control. The mismanagement of MDR-TB cases could lead to an increase in the far more difficult to treat extensively drug-resistant TB (XDR-TB), which is already of great concern worldwide. Enhanced prevention and control efforts are urgently needed in order to stem the continued spread of MDR-TB.

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