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Current status and future trends in the diagnosis and treatment of drug-susceptible and multidrug-resistant tuberculosis

Suhail Ahmad*, **Eiman Mokaddas**

Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait

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Summary The global burden of tuberculosis (TB) is still large. The increasing incidence of drug-resistant, multidrug-resistant (MDR) (resistant to at least rifampicin and isoniazid), and extensively drug-resistant (XDR) (additionally resistant to a fluoroquinolone and kanamycin/amikacin/capreomycin) strains of *Mycobacterium tuberculosis* and the association of active disease with human immunodeficiency virus coinfection pose a major threat to TB control efforts. The rapid detection of *M. tuberculosis* strains and drug susceptibility testing (DST) for anti-TB drugs ensure the provision of effective treatment. Rapid molecular diagnostic and DST methods have been developed recently. Treatment of drug-susceptible TB is effective in ≥95% of disease cases; however, supervised therapy for ≥6 months is challenging. Non-adherence to treatment often results in the evolution of drug-resistant strains of *M. tuberculosis* due to mutations in the genes encoding drug targets. Sequential accumulation of mutations results in the evolution of MDR and XDR strains of *M. tuberculosis*. Effective treatment of MDR-TB involves therapy with 5—7 less effective, expensive, and toxic second-line and third-line drugs for ≥24 months and is difficult in most developing countries. XDR-TB is generally an untreatable disease in developing countries. Some currently existing drugs and several new drugs with novel modes of action are in various stages of development to shorten the treatment duration of drug-susceptible TB and to improve the outcome of MDR-TB and XDR-TB.

* Corresponding author at: Department of Microbiology, Faculty of Medicine, AMAR Health Sciences Center, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait. Tel.: +965 2498 6503; fax: +965 2531 8454.
E-mail addresses: suhail_ah@hsc.edu.kw, suhail_ah2000@yahoo.com (S. Ahmad).

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Introduction

Despite a slow decline in the incidence of tuberculosis (TB) in recent years, the global burden of TB is still large. Active disease is mainly caused by *Mycobacterium tuberculosis*. The inhalation of droplet nuclei containing a few bacilli during close human contact with sputum smear-positive pulmonary TB patients results in new TB infections. However, primary infection with *M. tuberculosis* only leads to clinically active TB disease in ~10% of exposed individuals. In other immunocompetent hosts, an effective immune response arrests further multiplication of tubercle bacilli, but complete pathogen clearance is achieved by only a few individuals. The sub-optimal immune response of the remaining subjects only succeeds in containing the infection, as some bacilli escape killing and persist in a dormant state in granulomatous lesions. The latent infection may remain dormant for a long time; however, *M. tuberculosis* can reactivate and cause active TB, typically due to weakening of the immune system [1]. The World Health Organization (WHO) has estimated that one-third of the total world population is latently infected with tubercle bacilli and that 5—10% of infected individuals will develop active TB during their lifetime [1,2]. Reactivation of latent infection occurs more frequently (5—15% per year and ~50% over a lifetime) in human immunodeficiency virus (HIV)-coinfected individuals [3].

The reactivation of latent infection is largely responsible for active TB in countries with low TB incidence, while recent infection and re-infection are also common in countries with a high TB burden [2,4]. Major factors sustaining the global burden of TB include the increasing incidence of *M. tuberculosis* strain resistance to the most effective first-line and important second-line anti-TB drugs and the growing population of HIV-coinfected and other immunocompromised/immunosuppressed individuals with underlying conditions such as diabetes [2,3,5].

Global epidemiology of TB, drug-resistant TB, MDR-TB, and XDR-TB

According to annual WHO surveys, 8.7 million new and relapse cases of active TB (estimated incidence of 125 per 100,000 population) occurred in 2011 [2]. Nearly 1.1 million (13%) TB patients were coinfected with HIV. The estimated cases mostly occurred in Asia (59%) and Africa (26%). Approximately 7.7%, 4.3%, and 3% of cases occurred in the Eastern Mediterranean region, the European region, and the Region of the Americas, respectively. The 22 countries with a high TB burden accounted for 82% of all cases, while the highest incidence rate (262 per 100,000 population) was recorded for the African region, mainly due to a higher prevalence of HIV coinfection. Globally, the 12 million TB cases in 2011 resulted in 1.4 million deaths (including 430,000 among HIV-coinfected individuals) [2].

The WHO has also collected drug susceptibility testing (DST) data for the isoniazid (INH), rifampicin (RIF), ethambutol (EMB), and streptomycin (SM) first-line drugs. Phenotypic DST for another first-line drug, pyrazinamide (PZA), is not routinely performed because the drug is active at acidic pH values, which complicates susceptibility testing [6]. Recent data showed that resistance to at least one anti-TB drug (defined as any resistance) was 11.1% among new TB cases and was higher