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The global tuberculosis situation and the inexorable rise of drug-resistant disease☆

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ABSTRACT

The highly cost-effective DOTS strategy helped to bring the global tuberculosis (TB) epidemic under control in many parts of the world; however, the emergence and spread of drug-resistant strains pose a major threat to these gains. Molecular epidemiology studies, together with recent genomic evidence, provide proof that some drug-resistant strains are highly transmissible with documented epidemic spread. The potential for epidemic replacement of drug-susceptible with drug-resistant strains provides strong motivation for renewed emphasis on TB drug and vaccine development. It also reflects the need for enhanced infection control measures in health care and congregate settings, especially in TB endemic areas. The exploration of preventive therapy options for close contacts of patients with infectious drug-resistant TB also warrants further exploration, in an attempt to break the transmission cycle. Increased population mobility and large scale cross-border migration imply that the inexorable rise of drug-resistant TB is not geographically confined; it is a global concern that poses a very real threat to TB endemic and non-endemic settings. Failure to find new solutions will compromise traditional TB control efforts and derail momentum toward future TB elimination.

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1. Introduction

Mycobacteria have a unique lipid-rich cell wall, which explains their 'acid-fast' property and renders them resistant to many disinfectants and antibiotics. Among mycobacteria, *Mycobacterium tuberculosis* is a

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major pathogen that is fully adapted to the human host. Although effective treatment is available, acquired drug-resistance was documented shortly after streptomycin was introduced in the 1940s. The same happened with the use of isoniazid monotherapy, followed by evidence that these drug-resistant strains were transmitted within the community [1]. Subsequent studies indicated that the acquisition of drug resistance can be minimized by adherent, quality-assured multi-drug therapy, which provided the rationale for the DOTS strategy. The DOTS strategy emphasized the importance of using standardized multi-drug regimens with uninterrupted supply of quality-assured drugs and ensuring strict treatment adherence through directly observed therapy (DOT). By 2010, world-wide DOTS implementation cured more than 50 million patients and averted more than 7 million deaths compared to pre-DOTS standards [2], but it was ill equipped to deal with the growing contribution of transmitted drug-resistant tuberculosis (TB). This review summarizes the rise of drug-resistant TB, explores the factors driving this rise and highlights consequences for global TB control and elimination efforts.

2. The rise of drug resistant TB

The global burden of drug resistant TB remains poorly quantified, since routine sputum smear microscopy is unable to differentiate drug-resistant from susceptible strains. Better access to rapid molecular tests, such as the Xpert MTB/RIF® assay, and traditional phenotypic drug susceptibility testing (DST), as well as prevalence surveys conducted in many high burden settings are slowly improving data quality. The World Health Organization (WHO) estimates that 9.6 million people developed TB in 2014, of whom 480,000 (5%) had multidrug resistant (MDR; resistance against isoniazid and rifampicin) disease [3]. Table 1 provides a brief overview of the first- and the second-line TB drugs that provided the mainstay of TB treatment under the DOTS strategy. The Xpert MTB/RIF® assay simultaneously detects the presence of the rpoB gene, which is specific for *M. tuberculosis complex*, as well as mutations in the gene that indicate rifampicin resistance, which serves as a proxy for MDR-TB.

The highest MDR-TB case-loads exist in the Indian subcontinent, China, the Russian Federation and Southern Africa; (Fig. 1) accounting for more than 60% of cases globally [3,4]. However, the emergence of drug-resistant TB is not restricted to these locations and extremely drug resistant (XDR; MDR with additional resistance to fluoroquinolones and second-line injectable agents) TB has now been reported in more than 100 countries; treatment access and outcome remain poor (Fig. 2) [3]. India is the first country to have reported cases with so-called "totally drug resistant" TB [5]. Although the term "totally drug resistant" is difficult to define, the management of patients who are untreatable without access to novel TB drugs poses a major clinical dilemma. National drug-resistance surveys have been completed during 2014/5 in India and China (Fig. 3); formal results are eagerly awaited. A previous drug resistance survey conducted in China in 2007 reported MDR-TB among 5.7% of new and 25.6% of re-treatment TB cases [6], with high rates of concurrent fluoroquinolone resistance [7]. A recent analysis of 100 pediatric specimens held in the strain library of the Chinese Centre for Disease Control and Prevention demonstrated high rates of drug resistance; any drug resistance in 55% and MDR in 22% [8]. This is alarming, since children with drug-resistant TB generally provide an indication that these strains are actively transmitted within the community.

The possibility of epidemic replacement, where drug resistant strains pre-dominate over drug susceptible strains, is illustrated by parts of the Russian Federation where over 30% of newly diagnosed cases have MDR-TB [3]. The highest rates have been reported in Minsk, Belarus, where almost half of new and more than three quarters (75.6%) of previously treated TB cases were diagnosed with MDR-TB during 2011 [9]. Africa represents the epicenter of the dual human immunodeficiency virus (HIV) and TB epidemic, with more than 50% of adult TB cases having HIV co-infection in many sub-Saharan countries. TB/HIV co-infection rates exceeding 80% have been reported from Swaziland, with high rates of MDR-TB among co-infected patients [10]. Particularly problematic is the occurrence of an *rpoB*1419F mutation that is not detected by the Xpert MTB/RIF® assay, raising concerns that delayed MDR-TB diagnosis might facilitate transmission among immune compromised patients in Swaziland [10]. Similar to Swaziland, many smaller countries struggle with high rates of TB and MDR-TB, but they have limited visibility on the international stage due to relatively low absolute case numbers.

Table 1
First- and second-line drugs used in the treatment of tuberculosis.

Group	Drug
Treatment of drug-susceptible TB	
Group 1	Isoniazid
First-line oral agents (Regimen 1)	Rifampicin
	Ethambutol
	Pyrazinamide
Additional injectable agent used for retreatment cases* (Regimen 2)	Streptomycin
Additional treatment options for drug-resistant TB	
Group 2	Kanamycin
Injectable agents	Amikacin
	Capreomycin
	Streptomycin
Group 3	Moxifloxacin
Fluoroquinolones	Levofloxacin
	Ofloxacin
Group 4	Ethionamide
Oral bacteriostatic agents	Prothionamide
	Cycloserine
	Terizidone
	Para-aminosalicylic acid
Group 5	Clofazimine
Agents with unclear efficacy or concerns regarding usage	Linezolid
	Amoxicillin-clavulanic acid
	Thiacetazone
	Imipenem/ Meropenem
	High dose isoniazid
	Clarithromycin
New agents	Bedaquiline
	Delamanid

* The addition of a single drug (streptomycin) to patients who fail first-line treatment or present with a second episode of TB does not have a strong rationale and is not supported by evidence, but it is still used in many countries.

High and rising rates of drug-resistant TB have relevance beyond the worst affected areas, since TB does not respect national borders, spreading through people movement and regular social contact. Western Europe, Australia, the USA and other developed countries receive millions of travelers from East and Southeast Asia, Eastern Europe and Africa each year, while migrants from these areas maintain regular contact with their country of origin. Populations have become highly mobile in a globalized world with bidirectional movements between countries linked to economic and tourist activity, as well as appeals for safe refuge. Even with meticulous pre-entry screening the vast majority of TB cases in non-endemic areas occur among recent immigrants, migrant workers and international students [11]. Screening for latent *M. tuberculosis* infection would be further compromised if prophylactic treatment options lose their efficacy in individuals harboring MDR-TB strains. With current diagnostic tests it is impossible to identify latent infection with an MDR strain, or to detect a re-infection event in someone who visited a TB endemic area. These findings emphasize the need for improved epidemiological understanding, including better description of the evolution and transmission dynamics of drug-resistant *M. tuberculosis* strains.

3. Factors driving the rise

3.1. Epidemic spread

Although observations from the 1950s confirmed the transmissibility of clinical drug-resistant strains [1], these observations were

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