

# Extensively drug-resistant (XDR) tuberculosis: an old and new threat

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**Summary.** Tuberculosis (TB) remains a worldwide emergency (8 million new cases per year, 2 million deaths annually) mostly affecting poor countries. To this old, persistent threat, a new emergency is adding further challenge, *i.e.*, the multidrug-resistant TB, which in its extreme and highly lethal form is called XDR TB (extensively drug-resistant TB). How to fight XDR TB is a high research and public health priority.

*Key words:* *Mycobacterium tuberculosis*, drug susceptibility testing, first-line drugs, second-line drugs, drug resistance.

**Riassunto** (*Tubercolosi estrema: una vecchia e nuova minaccia*). La tubercolosi (TB) continua ad essere una emergenza mondiale (8 milioni di nuovi casi all'anno, 2 milioni di morti) che colpisce soprattutto i paesi poveri. A questa vecchia minaccia si associa una nuova emergenza, la TB multiresistente che nella sua forma di resistenza estrema, altamente letale, è detta appunto "TB estrema". Come combattere questa nuova minaccia è diventata una assoluta priorità di ricerca in sanità pubblica.

*Parole chiave:* *Mycobacterium tuberculosis*, farmaci di prima linea, farmaci di seconda linea, farmacoresistenza.

## INTRODUCTION

Tuberculosis (TB) remains a deadly infectious disease affecting millions of people worldwide, with 95% of cases and 98% of deaths occurring in developing countries [1]. The World Health Organization (WHO) recommends, within the New Stop TB Strategy, standardized TB treatment regimens based on short-course chemotherapy. The anti-TB drug regimen recommended for the treatment of new cases consists of two months of isoniazid (INH), rifampin (RMP), and pyrazinamide (PZA), plus a fourth drug (streptomycin, SM, or ethambutol, EMB), followed by four months of INH and RMP, *i.e.*, the two most powerful first-line anti-TB drugs [2]. This treatment is usually effective against wild *Mycobacterium tuberculosis* (Mtb) strains that have never been exposed to anti-TB drugs for more than 30 days. However, since this therapy lasts at least 6 months, inappropriate treatment is rather frequent especially in developing countries, increasing the likelihood of selecting Mtb strains resistant to one or more drugs. Exposure to an insufficient number of drugs as a result of poor adherence to treatment, inappropriate prescription, irregular drug supply, and/or poor drug quality, suppresses the growth of bacilli susceptible to one or more drugs, but permits the multiplication of naturally pre-existing drug-resistant organisms, thus selecting for drug resistant bacteria [1].

## MULTIDRUG-RESISTANT TUBERCULOSIS

In recent years, a dramatic increase in the emergence of multidrug-resistant (MDR) Mtb strains, *i.e.* strains resistant at least to INH and RMP, has been observed. Isolation of MDR strains was reported as a major problem particularly in former Soviet Union countries [3, 4], but also in other poor areas of the world [5]. The WHO estimated the annual burden of MDR TB to be 300 000-600 000 cases and the prevalence of MDR TB to be threefold higher than the annual incidence, primarily in low and middle-income countries [6]. In contrast, MDR TB in countries with good national control programs such as in Western Europe, is not a major health problem. In Italy, the prevalence of MDR TB among new cases in the period 1998-2001 was 1.1% [7].

Patients with MDR strains should receive therapy based on individual drug susceptibility testing (DST), including residual first-line (SM, EMB, PZA) and second-line drugs (SLD) such as ofloxacin, kanamycin, capreomycin, ethionamide, *p*-aminosalicylic acid, and cycloserine. As with other antimicrobial agents, the use of SLD can generate resistant mutants. *In vitro* SLD DST often shows poor reproducibility and lack of correlation with clinical response. Nevertheless, many laboratories perform DST [8], and molecular methods allowing rapid diagnosis of resistance to the fluoroquinolones (the most potent SLD) have been developed [9].

### XDR TB: DEFINITION

In 2000, the WHO Stop TB partnership's Green Light Committee, created to increase access to SLD worldwide, met several reports of multiple cases of TB with resistance to virtually all second-line drugs [6]. In 2000-2004, the WHO and the Centers for Disease Control (CDC) surveyed a total of 17 690 TB isolates and, in a report jointly published in March 2006, showed that 20% of those isolates were MDR and 2% were strains extensively drug-resistant (XDR) to SLD [6]. In addition, population-based data from United States (for 1993-2004), Latvia (for 2000-2002), and South Korea (for 2004) showed that 4%, 19%, and 15%, respectively, of MDR TB cases, were XDR [6].

The term XDR (also referred to as extreme drug resistance) TB was used for the first time in November 2005 [10, 11] and provisionally defined as TB cases in persons harboring *Mtb* strains resistant *in vitro* to at least INH and RMP (MDR definition) among first-line drugs, and to at least three or more of the six main classes of second-line drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and *p*-aminosalicylic acid). Subsequent reports suggested different definitions for XDR TB [12]. In October 2006 the WHO, also in consideration of the difficulty to test some SLD [8] and the fact that some forms of drug resistance are less treatable than others, revised the definition. XDR TB was defined as resistance to at least INH and RMP in addition to resistant to any fluoroquinolone, and to at least one of the three injectable second-line drugs (amikacin, capreomycin, or kanamycin) [12].

### XDR TB: SPREAD

In March 2006 report, the WHO-CDC documented the presence of XDR TB in 17 countries [12, 13]. More recent studies described at least one case of XDR TB in Argentina, Armenia, Bangladesh, Brazil, Chile, Czech Republic, Ecuador, France, Georgia, Germany, Italy, Republic of Korea, Latvia, Mexico, Peru, Portugal, Russian Federation, South Africa, Spain, Thailand, the UK and the USA [14]. Other data on XDR TB have been reported from Iran [15], Australia [16], Italy and Germany [17]. In a survey performed by our group from September 2000 to April 2004 in Abkhazia, a former Soviet Union Caucasian region on the Black Sea coasts, XDR TB was found in 1 out of 63 MDR *Mtb* strains (1.6%) [4].

The largest outbreak of XDR TB is certainly the one that occurred in an HIV-positive population in the KwaZulu-Natal region in South Africa, characterized by a high mortality rate [18, 19]. Out of 544 patients studied, 221 had MDR TB; of these, 53 were defined as XDR TB. Of the 53 patients, 44 had been tested for HIV and all were HIV-positive; 52 of 53 patients died, on average, within 25 days, including those treated with antiretroviral drugs (<http://www.who.int/mediacentre/news/notes/2006/np23/en/index.html>). Due to the high prevalence of HIV in South Africa, XDR TB is a problem much

more difficult to manage than in Eastern Europe and South-East Asia. XDR TB is difficult to cure and treatment requires that all six classes of SLD are available to clinicians. Instead, the majority of South African patients have yet to access to many SLD, including capreomycin, moxifloxacin, *p*-aminosalicylic acid, or adjunctive thoracic surgery [20]. To confront XDR TB it is then necessary to improve strategies in that country, focusing on more rapid diagnosis, better access to drugs and adherence to treatment, decentralization of primary care level services [21]. Overall, XDR TB is associated with elevated mortality, and is currently considered one of the most challenging threats for public health.

### XDR TB: MANAGEMENT AND CONTROL

Drug resistant TB results largely from poorly managed care of TB. If first-line anti-TB drugs are misused or mismanaged, MDR TB can develop. MDR TB needs to be treated with SLD and XDR TB can develop when SLD are also misused or mismanaged, thus becoming ineffective (<http://www.who.int/tb/xdr/faqs/en/index.html>). In consideration of the widespread use of SLD, in particular of fluoroquinolones (also used for other diseases such as respiratory tract infections), the emergence of XDR TB is then not surprising in countries with poor control practices [22]. In most of the world XDR TB seems to have appeared among HIV-seronegative individuals [17]. The occurrence of the South Africa outbreak in HIV/AIDS affected people is a serious concern because of the high mortality rate. The difficulty to manage an outbreak of MDR TB in HIV-infected people was experienced in the 1990s in the US and other countries, including Italy [23, 24], due to the rapid progression to death and high spreading of the strains among other immunosuppressed individuals. Indeed, in Europe and other countries where the majority of XDR TB cases develop among HIV-negative persons, the disease usually presents a more chronic evolution [17], thus being still associated with elevated mortality.

The WHO Global Task Force on XDR TB met in Geneva on 9-10 October 2006 (<http://www.who.int/mediacentre/news/notes/2006/np29/en/index.html>) and indicated seven recommendations mainly focusing on strengthening of TB and HIV control, management of XDR TB suspects, treatment design, laboratory definition, protection of health care workers, surveillance, advocacy, communication and social mobilization. In practice, one of the first priorities is to diagnose rapidly and correctly XDR TB. This means to increase the laboratory capacity, *e.g.*, to allow the reference laboratories in each country to perform correctly DST for all the SLD necessary to diagnose XDR TB. In order to evaluate DST of a clinical isolate by traditional methods, the bacteria need to be cultivated and tested with drugs: between 6 and 16 weeks are necessary to confirm the diagnosis. To reduce the time for diagnosis, molecular tests

to rapidly identify INH and RMP resistance should be introduced in the laboratory, together with drug susceptibility testing for SLD, but large investments in personnel and facilities are necessary.

## CONCLUSIONS

Overall, the emergence of XDR TB is a reminder that TB control globally needs a massive commitment by scientific, political and financial authorities [22]. WHO strategy has rightly called to the above ac-

tions. Nonetheless, a better control if not the elimination of TB and its deadly association with MDR or XDR TB will be achieved only when new diagnostic, therapeutic and, more importantly, a vaccine breaking the contagious phase of pulmonary TB will be generated and correctly used. The ISS and Stop-TB associations are strongly advocating this line of thinking and research.

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