

Extensively drug-resistant tuberculosis

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Purpose of review

To describe the origin, epidemiology, diagnosis, treatment, prevention, and control of extensively drug-resistant tuberculosis (XDR TB).

Recent findings

XDR TB is defined as the occurrence of TB in persons whose *Mycobacterium tuberculosis* isolates are resistant to isoniazid and rifampin and to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). As of June 2008, XDR TB has been found in 49 countries including the United States. It generally takes several weeks to detect XDR TB using conventional culture-based methods, although some progress is being made in developing rapid molecular tests. Treatment for XDR TB is difficult, usually requiring at least 18–24 months of four to six second-line anti-TB drugs. Treatment success rates are generally 30–50%, with very poor outcomes in HIV-infected patients. Management of contacts to infectious XDR TB patients is complicated by the lack of a proven effective treatment for XDR latent tuberculosis infection.

Summary

XDR TB is an emerging global health threat. The disease is difficult and expensive to diagnose and treat, and outcomes are frequently poor. New rapid diagnostic tests and new classes of anti-TB drugs are needed to successfully combat this global problem.

Keywords

extensively drug-resistant tuberculosis, multidrug-resistant tuberculosis, tuberculosis

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Introduction

Globally, there are approximately 9 million new tuberculosis (TB) cases every year. This number continued to increase through 2006, although the case rate per 100 000 persons appeared to be leveling [1^{*}]. Over the past two decades, two major obstacles to global tuberculosis control have emerged. The first is the high prevalence of HIV among TB patients in certain regions, especially sub-Saharan Africa, and the second is the growing problem of anti-TB drug resistance. In addition to increasing numbers of cases of drug resistance, strains of *Mycobacterium tuberculosis* (MTB) have become resistant to an increasing number of drugs. MTB strains resistant to the most effective first-line and second-line drugs have emerged that verge on being untreatable. The term extensively drug-resistant TB (XDR TB) is used to characterize disease caused by such highly resistant strains. This review will describe the origin, epidemiology, diagnosis, treatment, prevention, and control of XDR TB.

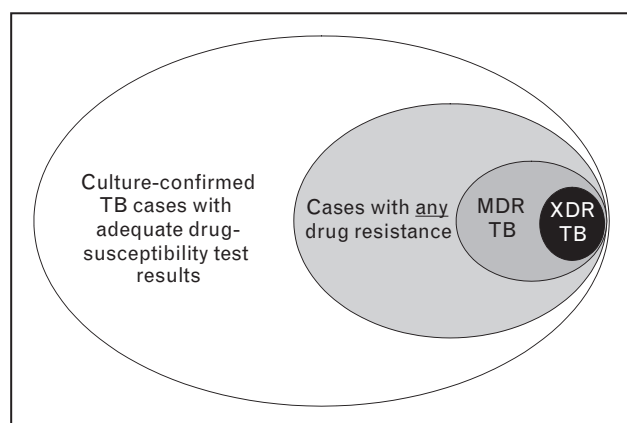
Recognition and definition of extensively drug-resistant tuberculosis

Beginning in the 1990s, anti-TB drug resistance became a significant problem in the United States and other parts of the world with the advent of multidrug-resistant TB (MDR TB). MDR TB is defined as TB caused by MTB that is resistant to at least the two best first-line medications, isoniazid and rifampin. Beginning in 2000 in response to reports of MDR TB that was also resistant to many second-line drugs, the US Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the International Union Against Tuberculosis and Lung Disease conducted a survey of a network of 25 supranational mycobacterial reference laboratories [2^{**},3]. The survey found that approximately 10% of MDR TB isolates were also resistant to three of six classes of second-line drugs. TB caused by MTB strains with this resistance pattern was termed XDR TB. The report of the survey also examined treatment outcomes from Latvia and the United States and found

that patients with XDR TB had worse outcomes than patients who had MDR TB that was not XDR.

In 2006, investigators working in KwaZulu Natal, South Africa, reported on an XDR TB outbreak, primarily among patients also infected with HIV [4]. They found 221 patients with MDR TB, of whom 53 had XDR TB. Of 53 patients with XDR TB, 52 (98%) died with a median survival of 16 days. Of 44 patients tested for HIV, all were infected. Most of the patients had not received previous treatment for TB and genotyping showed 85% had similar strains, suggesting much of the drug resistance was being transmitted rather than being acquired during treatment. In response to the outbreak, the South African Medical Research Council, with the support of CDC and WHO, held an expert consultation on XDR TB, which was followed by a WHO Global Task Force on XDR TB. On the basis of these consultations, the definition of XDR was revised. XDR TB is currently defined as the occurrence of TB in persons whose MTB isolates are resistant to isoniazid and rifampin (MDR TB) and to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin) (Fig. 1) [5]. The revision was based on two factors. First, drug-susceptibility test results for fluoroquinolones and second-line injectable drugs are more reproducible and reliable than for other second-line drugs. Second, review of unpublished data revealed that resistance to fluoroquinolones and second-line injectable drugs was associated with especially poor treatment outcomes [6•].

Figure 1 Extensively drug-resistant tuberculosis is a subcategory of multidrug-resistant tuberculosis



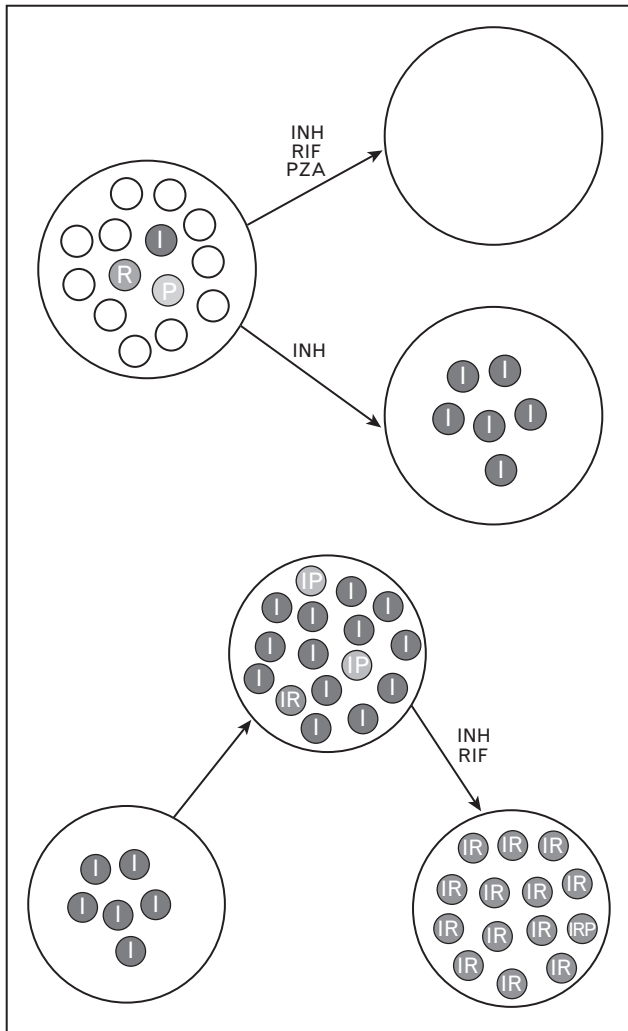
Multidrug-resistant tuberculosis (MDR TB) is defined as TB caused by *Mycobacterium tuberculosis* (MTB) that is resistant to at least the two best first-line medications, isoniazid and rifampin. Extensively drug-resistant tuberculosis (XDR TB) is TB caused by MTB that is resistant to isoniazid and rifampin (MDR) and to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). Reproduced from original figure provided by Dr Peter Cegielski.

Etiology of drug-resistant tuberculosis

In individual mycobacteria, drug resistance results from spontaneous genetic mutation [7]. Even though the rate of spontaneous mutations is low (several mutations per million organisms or fewer), patients with advanced TB have a very large burden of organisms. Therefore, thousands of mutants resistant to an individual drug may be present. With prolonged exposure to a single drug, the subpopulation of organisms resistant to that drug will be selected, expand, and become dominant (Fig. 2). This phenomenon is termed acquired drug resistance. Consequently, TB must be treated with at least two drugs to which the organism is susceptible [8]. Failure of patients to take all medications as prescribed or failure of physicians to prescribe an adequate regimen can result in drug resistance. In developing countries, drug shortages, interruptions in drug supplies and poor quality drugs also contribute to the development of drug resistance [9]. Therefore, the greatest risk factor for the presence of MDR TB is a history of prior treatment for TB [10,11]. Patients with TB from US communities or foreign countries with high MDR TB rates are also at increased risk [10–12]. XDR TB generally occurs because drug resistance is amplified through inadequate treatment of MDR TB. Drug-resistant TB may also be transmitted directly from a contagious patient to another person. Persons who contract drug-resistant tuberculosis in this manner have what is called primary drug resistance [10]. A significant portion of the KwaZulu Natal outbreak described above appears to have resulted from person-to-person transmission of XDR TB, that is, an example of primary drug resistance [4].

Epidemiology of extensively drug-resistant tuberculosis

As of June 2008, XDR TB has been detected in 49 countries. In the fourth WHO anti-TB drug resistance report, covering the years 2002–2007, the prevalence of XDR TB was found to be highly variable [13••]. As a percentage of MDR TB cases, XDR TB ranged from 0% in Rwanda and Tanzania to 12.8% in Baku, Azerbaijan, 15% in Donetsk, Ukraine and 23.7% in Estonia. In absolute reported cases, XDR TB was found to be generally less common in Western and Central Europe, the Americas and East Asia, but more of a problem in Eastern Europe and the former Soviet republics of Central Asia. Overall, of MDR TB cases reported to WHO that had adequate second-line drug-susceptibility testing, 7% were XDR TB. Although global trend data for XDR TB incidence are not available, based on the fact that there is an increase in the estimated annual global MDR TB incidence from approximately 270 000 in 2000 to 490 000 in 2006, it can be surmised that the XDR TB incidence is also increasing [13••,14].

Figure 2 How anti-TB drug resistance occurs

A small fraction of *Mycobacterium tuberculosis* organism will experience spontaneous genetic mutations that confer drug resistance (drug-susceptible organisms are represented by empty circles; naturally occurring drug-resistant organisms are marked with an 'I' for isoniazid resistant, an 'R' for rifampin resistant and a 'P' for pyrazinamide-resistant). In the first panel, use of a multidrug treatment regimen kills all the organisms (upper arrow). However, treatment with a single drug, isoniazid leads to selection and dominance of isoniazid-resistant organisms (lower arrow). In the second panel, the dominant isoniazid-resistant organisms undergo additional spontaneous mutations such that some now become multidrug resistant. Treatment with isoniazid and rifampin kills the organisms that are isoniazid monoresistant, but fails to kill the organisms that are multidrug resistant, which proliferate and become dominant. Reproduced from original figures developed by Drs Patricia Simone and Samuel Dooley.

From 1993 through 2006, 49 cases of XDR TB were reported in the United States [15^{••}]. This accounted for 3% of MDR TB cases that had sufficient drug-susceptibility test results to confirm or exclude XDR TB. Thirty of the 49 cases were reported from two states (New York and California). Data were stratified based

on two periods, 1993–1999 (a period of rapid decline in TB incidence in the United States following implementation of interventions to prevent and control the unprecedented resurgence of TB, including HIV-associated MDR TB in 1985–1992) and 2000–2006 (a period of slower decline in TB incidence). During the first period, most persons with XDR TB were US born (59%) and a high percentage was HIV infected (44%). During the second period, most persons with XDR TB were foreign born (76%) and a few were HIV infected (12%).

Diagnosis of extensively drug-resistant tuberculosis

The diagnosis of XDR TB requires obtaining an isolate of MTB from sputum or another specimen of body fluid or tissue and testing the isolate for susceptibility to anti-TB drugs. The gold standard for drug-susceptibility testing is the agar proportion method [16,17[•],18^{••}]. However, liquid culture methods are reliable and more rapid for first-line drugs [16,17[•],18^{••}]. Drug-susceptibility testing for fluoroquinolones and second-line injectable drugs is more reproducible and reliable than for other second-line drugs. A major problem is that conventional culture-based methods take 3–4 weeks to identify drug resistance, leading to delays in patients being placed on appropriate therapy.

The identification of specific mutations in the MTB genome that confer resistance to anti-TB drugs has led to the development of molecular assays for drug resistance. The advantage of using molecular assays is that results can be available in hours. Mutations in the *rpoB* gene of MTB account for greater than 95% of rifampin resistance (Table 1) [17[•],18^{••}]. In addition, because isolated rifampin resistance is rare, identification of these mutations serves as a good surrogate for identification of MDR TB. The line-probe assay for rifampin resistance has been shown to be very sensitive ($\geq 97\%$) and specific ($\geq 98\%$) when used on either isolates from culture or direct respiratory specimens that are acid-fast bacillus smear positive [19^{••},20[•]]. Commercial versions of this test exist, but are not currently approved for use in the United States. One of the line-probe assays, GenoType MTBDRplus (Hain Lifescience, GmbH, Nehren, Germany), also tests for isoniazid resistance with 84% sensitivity and 99% specificity [19^{••}]. Although mutations in MTB genes conferring resistance to many other first-line and second-line drugs have been identified, they do not account for all of the drug resistance found by conventional methods (Table 1) [17[•],18^{••}]. This suggests that not all genetic mutations involved in anti-TB drug resistance have been discovered. In addition, standardized assays have not been developed to detect many of the known mutations.

Table 1 Genetic mutations of *Mycobacterium tuberculosis* that confer drug resistance

Antituberculosis drug	Gene mutated	Percentage of mutations	Product of that gene
Isoniazid	<i>katG</i>	40–60	Catalase-peroxidase (activates INH)
Isoniazid – ethionamide	<i>inhA</i>	15–43	Reductase analog (Mycolic acid synthesis)
Isoniazid	<i>ahpC</i>	10	Hydroperoxidase reductase
Isoniazid	<i>kasA</i>	Unknown	Carrier protein synthase
Rifampin	<i>rpoB</i>	>96	Subunit of RNA polymerase
Pyrazinamide	<i>pncA</i>	72–97	Pyrazinamidase
Ethambutol	<i>embB</i>	47–65	Arabinosyltransferase
Streptomycin	<i>rpsL</i>	70	Ribosomal protein S12
Streptomycin	<i>rrs</i>	70	16S rRNA
Fluoroquinolones	<i>gyrA</i>	75–94	DNA gyrase A subunit

Data from [18**].

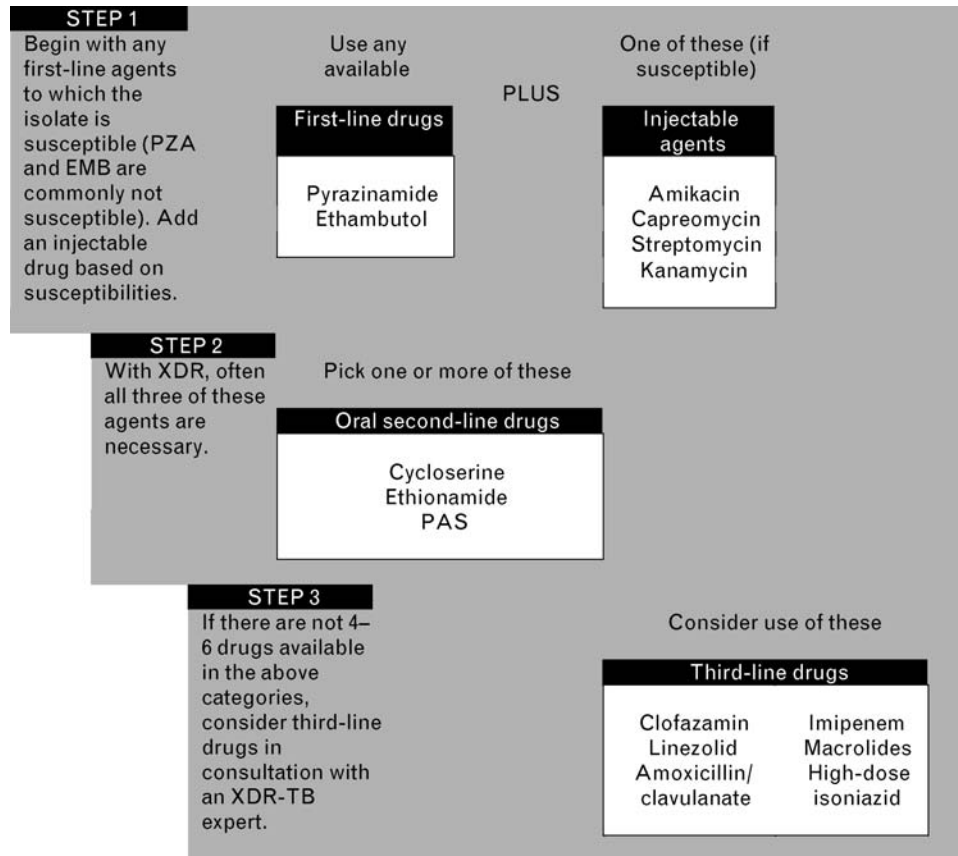
Treatment of extensively drug-resistant tuberculosis

Standard treatment for drug-susceptible TB consists of INH, rifampin, and pyrazinamide for 6–9 months (pyrazinamide is used only for the first 2 months; ethambutol is also used until susceptibility to INH and rifampin is confirmed). Treatment is highly effective with a greater than 95% success rate and has been validated through randomized controlled trials [8]. Treatment for MDR TB is longer (at least 18–24 months) and includes the use of second-line drugs that are more expensive and toxic, but less effective. Observational studies have shown that success rates are substantially lower than for drug susceptible TB. Even in the most favorable setting, the overall long-term treatment success rate is 75% [21]. Of note, improved treatment outcomes have been associated with fluoroquinolone use, which has obvious implications for patients with XDR TB [21]. Outcomes in less favorable settings, especially where many of the patients are HIV-infected, have been considerably worse [18**].

Specific XDR TB outcome data are relatively sparse, but success rates tend to be quite poor and approach those of the preantibiotic era. In particular, HIV-infected XDR TB patients have very high mortality rates. Of the 49 patients with XDR TB reported in the United States (1993–2006), only 17 (35%) completed therapy and 12 (29%) died [15**]. Ten of 12 patients who died were HIV infected. European investigators examined outcomes of XDR TB patients from Italy, Germany, Estonia, and the Russian Federation (2003–2006). Of 48 XDR TB patients with treatment outcomes, only 22 (46%) were successfully treated, 12 (25%) failed treatment, and 14 (29%) died [22**]. An analysis of XDR TB patients from South Korea found that of 43 patients, 23 (54%) were treated successfully, 14 (33%) failed or defaulted, and six (14%) died [23**]. None of the South Korean patients was HIV infected. In contrast, as previously described, XDR TB patients in KwaZulu Natal, South Africa, most (if not all) of whom were HIV infected, had a 98% mortality rate [4].

As XDR TB is a subcategory of MDR TB, the treatment principles are similar [8,18**]. Treatment of MDR TB and XDR TB is very complex and should only be done by or in consultation with an expert. A regimen of four to six anti-TB drugs to which the patient's MTB isolate is susceptible should be used. A three-step approach to selecting drugs, as shown in Fig. 3, is recommended. For pulmonary XDR TB, response to therapy is monitored by collecting sputum specimens for acid-fast bacillus smear microscopy and mycobacterial culture at least monthly throughout the course of treatment, which is 18–24 months after conversion of cultures to negative. Patients who do not convert their sputum cultures within the first 2–4 months of treatment are more likely to fail therapy [24]. Monitoring for relapse should continue by collecting specimens at least several times for the 2 years following completion of therapy. Second-line anti-TB drugs have numerous toxicities, which can be severe and even fatal. Monitoring for drug toxicity is based on the individual regimen. Some experts also find monitoring serum drug concentrations to be useful, but there is no consensus. To ensure adherence to treatment, use of patient-centered directly observed therapy (i.e., having a trained healthcare worker observe the patient take every dose of medication) enhanced with incentives and enablers is mandatory [8,25,26].

Treatment of XDR TB may also include surgical resection. One observational study of MDR TB demonstrated that patients who had surgery were more likely to have a successful treatment outcome [21]. In general, surgery should be considered if the patient's sputum cultures remain positive after 4–6 months on the best possible medical treatment or the pattern of drug resistance is such that the patient is not likely to be cured by medication alone [18**]. In addition, the best surgical candidates will have focal disease such that the remaining lung tissue will be relatively disease free after lobectomy or pneumonectomy. The surgery should be performed by a surgeon with experience in lung resections for TB and preferably after culture conversion, but at least after several months of therapy [18**]. A full course of medical treatment should be continued after surgery.

Figure 3 Stepwise process for building a treatment regimen for extensively drug-resistant tuberculosis

Extensively drug-resistant tuberculosis (XDR TB) should be treated with four to six drugs to which the *Mycobacterium tuberculosis* isolate is susceptible. Patients with XDR TB should be treated by or in close consultation with an XDR TB expert. Based on a figure in [18**].

Additional prevention and control measures for extensively drug-resistant tuberculosis

As for drug-susceptible TB, the primary strategy for controlling and preventing XDR TB is rapid diagnosis of and initiation of treatment for patients with the disease [27]. However, because therapy for XDR TB is much less effective, use of secondary prevention and control measures assumes greater importance. In this regard, patients with pulmonary XDR TB may need to be placed in respiratory isolation and remain in isolation longer than is necessary for patients with drug-susceptible TB. Depending on the setting, XDR TB patients may need to remain in respiratory isolation until their sputum cultures are negative [27,28]. For patients who fail to cooperate with respiratory isolation, legal action may be necessary [29].

In the United States, the second priority strategy for TB prevention and control is the identification of contacts of patients with infectious TB and treatment

with an effective drug regimen of those contacts that have been infected [27]. The lack of a proven effective regimen for treatment of MDR and XDR latent tuberculosis infection (LTBI) substantially impairs implementation of this strategy for MDR and XDR TB. Nevertheless, contacts of patients with XDR TB should be evaluated for LTBI using a tuberculin skin test or interferon-gamma release assay [such as QuantiFERON TB Gold (Cellestis, Victoria, Australia)]. TB should be excluded with further evaluation, including chest radiograph, for contacts with positive test results for LTBI or symptoms of TB. For those contacts with XDR LTBI, especially young children or those who are immunosuppressed, treatment for 6–12 months with two drugs to which the source patient's MTB isolate is susceptible may be considered [18**,30]. This recommendation is based strictly on expert opinion, as there are no efficacy data for any medications for the treatment of LTBI other than for isoniazid and rifampin. Regardless of whether contacts with XDR LTBI receive treatment, they should be monitored for signs

or symptoms of progression to TB disease for 2 years following infection [18^{••},30].

Given the problems encountered with treating XDR TB disease and LTBI, questions have been raised about the potential role of vaccination with Bacille Calmette-Guérin (BCG) in prevention and control of XDR TB. BCG vaccination in infancy is recommended globally by WHO for TB prevention, but has never been used routinely in the United States [31,32]. Clinical trials have demonstrated efficacy in preventing TB meningitis and disseminated TB in children, but the overall TB case reduction has been a highly variable 0–80% [33]. With regard to MDR (and therefore XDR) TB in the United States, currently BCG is recommended only in two situations [31]. First, BCG vaccination should be considered for an infant or child who is exposed continually to a patient who has infectious pulmonary MDR (and therefore XDR) TB when the child cannot be separated from the presence of the infectious patient. Second, BCG vaccination of healthcare workers (HCWs) should be considered on an individual basis in settings in which a high percentage of TB patients are infected with MDR (or therefore XDR) TB, transmission of such drug-resistant MTB strains to HCWs and subsequent infection are likely, and comprehensive TB infection-control precautions have been implemented and have not been successful.

The global response plan

In 2007, WHO produced a global response plan for MDR and XDR TB with eight objectives [34^{••}]. The objectives are to strengthen basic activities to control TB and HIV/AIDS to avoid additional emergence of MDR TB and XDR TB; scale-up the programmatic management of MDR TB and XDR TB; strengthen laboratory services for adequate and timely diagnosis of MDR TB and XDR TB; expand surveillance of MDR TB and XDR TB to better understand the magnitude and trends of drug resistance and the links with HIV; foster sound infection control measures to avoid MDR TB and XDR TB transmission to protect patients, HCWs, others working in congregate settings, and the broader community, especially in high HIV prevalence settings; strengthen advocacy, communication, and social mobilization for sustained political commitment and a patient-centered approach to treatment; pursue resource mobilization at global, regional, and country levels to ensure that necessary resources are available; and promote research and development into new diagnostics, drugs, vaccines, and operational research on MDR TB management to shorten the length of treatment. The plan is comprehensive and very ambitious and requires \$2.2 billion in funding for 2007–2008, of which only a small fraction had been secured at the time the report was issued.

Conclusion

In the long term, new tools will be needed if the global response to XDR TB is to be successful. Paramount among the required new tools is rapid diagnostic tests and new classes of anti-TB drugs. The development of accurate molecular diagnostic tests for rifampin resistance is a great step toward the rapid diagnosis of MDR TB. Similar tests are needed for fluoroquinolone and injectable drug resistance to rapidly detect XDR TB. Because of the poor treatment outcomes for XDR TB with current medications, new classes of effective anti-TB drugs are needed. Currently, there are only a handful of new anti-TB drugs in the pipeline and they are in early phases of development [35[•]]. The same is true for new vaccines. While we wait for new tools, we must make the most efficient use of existing TB-control and TB-prevention strategies with a particular focus on not creating additional cases of drug-resistant TB.

Acknowledgements

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There is no conflict of interests.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 209–210).

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