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Mycobacterial Infections (J Esteban, Section Editor)

Epidemiology of Tuberculosis and the Rise of XDR-TB

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Opinion statement

The global spread of multidrug-resistant strains of tuberculosis (TB) mycobacteria was one of the main reasons leading the World Health Organisation to launch the Stop TB program worldwide. In spite of a slow decline of TB incidence and mortality worldwide, multidrug-resistant TB (MDR-TB) has increased in several countries. MDR-TB is caused by organisms that are resistant to at least isoniazid and rifampicin. The most drug-resistant forms of TB are the extensively drug-resistant TB (XDR-TB) strains caused by organisms that are resistant also to fluoroquinolones and any of the second-line anti-TB injectable drugs. XDR-TB can take 2 years or more to treat with drugs that are less effective, more toxic, and more expensive. Mortality for XDR-TB is very high, and the risk of the transmission between persons of XDR-TB strains is a matter of concern for health systems. Major issues associated with enhanced XDR-TB are non-implementation of DOT (directly observed therapy) and DOT expansion strategies, the insufficient supply or the poor quality of the anti-tuberculosis drugs, and the inadequate intake of the anti-tuberculosis medicines. Nevertheless, prior treatment of MDR-TB with second-line drugs is the strongest associated factor increasing the risk for XDR tuberculosis more than fourfold. Specialized rapid, effective diagnostic methods, including drug-sensitivity testing, are essential for a precise diagnosis of XDR-TB, and subsequent proper treatment. The global rise and spread of XDR-TB have serious effects on TB-control programs, and urge effective health policy

responses. National TB control programmes working with all health services can prevent XDR-TB by ensuring that all the physicians and professionals caring for people with TB adhere to the International Standards for TB Care. Specialized centres at regional and national levels should be dedicated to care for difficult-to-treat and untreatable patients with XDR-TB.

Introduction

About 20 years ago, the World Health Organization (WHO) launched the Global Plan to Stop TB [1]. WHO developed the Stop TB strategy to contrast the challenging epidemiological trend of tuberculosis (TB) resurgence in the early 1990s due to the HIV epidemic, enhanced ease of global travel, and the spread of resistant strains of multidrug-resistant TB mycobacteria. Lacking an effective vaccine against TB, the WHO strategy focused on the prompt diagnosis and treatment of each TB case everywhere, particularly thanks to the diffuse adoption of directly observed treatment, or DOT, made accessible without barriers of gender, age, type of disease, social setting, or ability to pay. It was soon clear that the main global challenge to the DOT strategy was widespread TB organisms resistant to the antibiotics used in its treatment which heavily contributed to worldwide uncontrolled TB pandemics [2]. Table 1 resumes WHO's terminology of drug-resistant TB. Multidrug-resistant TB (MDR-TB) is caused by organisms that are resistant to at least the two most effective anti-TB drugs, isoniazid and rifampicin. Leading drug-resistant forms of TB are the extensively drug-resistant TB (XDR-TB) caused by organisms that are resistant to isoniazid and rifampicin (i.e. MDR-TB), as well as any fluoroquinolone and any of the second-line anti-TB injectable drugs (amikacin, kanamycin, or capreomycin). These forms of TB do not respond to the standard 6-month treatment with first-line anti-TB drugs and can take 2 years or more to treat with drugs that are less effective, more toxic, and more expensive. In a few countries, a totally drug resistant TB (TDR-TG) was also recognized, virtually resistant to all available first- and second-line anti-TB drugs [3, 4]. The emergence of TDR-TB has been identified in major publications, but not yet recognized by WHO [5, 6]. Just after 10 years from its launch, the multidimensional DOT strategy framework was implemented in 184 countries and led to >32 million patients receiving treatment and >25 million being cured [7, 8]. Despite successful results and real advances on the global control of TB deaths and infection, continued challenges to address effectively the epidemic arose from a number of people who continuously develop MDR-TB and XDR-TB worldwide [9, 10, 11•]. The increasing amounts of seriously diffuse TB drug resistance, especially XDR-TB, in a globalized environment in which local and international travel is easily available has led to a greater resolve among various governments and international organizations to act against the ongoing epidemic [12].

Table 1. World Health Organization terminology for drug-resistant TB

- ➢ Mono-resistant tuberculosis – TB caused by strains of Mycobacterium tuberculosis that are resistant only to a single anti-TB drug
- ➢ Poly-resistant tuberculosis – TB caused by Mycobacterium tuberculosis resistant to two or more drugs, but not isoniazid and rifampicin together.
- ➢ MDR-TB – TB caused by strains of Mycobacterium tuberculosis that are resistant at least to rifampicin and isoniazid.
- ➢ XDR-TB – Tb caused by Mycobacterium tuberculosis that are resistant to isoniazid, rifampicin, and at least one injectable second-line anti-TB drug and any of the fluoroquinolones.

Legend: MDR, multidrug-resistant; TB, tuberculosis; XDR, extensively drug-resistant

Global TB epidemiology after two decades of the "Stop TB" plan

WHO data reported that the incidence of TB is decreasing globally by approximately 2 % each year and TB-related mortality rate dropped 45 % between 1990 and 2012 [11•, 13]. An estimated 22 million lives have been saved through implementation of Stop TB Strategy using DOT recommended by WHO. There were an estimated 12 million cases (range, 10 to 13 million) of TB in 2011. The prevalence rate has fallen by 36 % globally since 1990. Regionally, prevalence rates are declining in all of WHO's regions, but mostly in the Americas, Western Pacific region, Southeast Asia, and Europe. Africa and Eastern Mediterranean regions have a slower decline of TB prevalence. However, even if the global estimated number of people falling ill with tuberculosis each year is declining, albeit very slowly, the global impact of TB is still too high in every part of the world. According to WHO data, TB is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. In 2012, 8.6 million people developed TB worldwide, a global incidence rate of 122 subjects per 100,000 people, and 1.3 million died. In 2012, an estimated 530,000 children became ill with TB and 74,000 HIV-negative children died of TB. Over 95 % of TB deaths occur in low- and middle-income countries, and it is among the top three causes of death for women aged 15 to 44 years. The incidence rates vary from highest in southern Africa (550/100,000 people in Zimbabwe and Mozambique, and 1,000/100,000 inhabitants in South Africa) to fewer than 10/100,000 people in Canada, USA, and most of western Europe [13]. It is a cause of concern that only two thirds of global incident TB cases have access to effective care because an estimated three million people with active TB are either not diagnosed or diagnosed, but not reported. The absolute number of cases is highest in Asia, with India and China having the greatest burden of disease globally [13, 14]. In the USA and most western European countries, the majority of cases occur in foreign-born residents and recent immigrants from high prevalence countries [15, 16]. However, the majority of incident cases occur in population-dense regions of Africa and Asia where HIV and TB are endemic [17, 18]. Furthermore, TB is a leading killer of people living with HIV causing one fifth of all deaths [11•, 18]. It should be taken into account that TB mortality among people who are HIV-positive is hard to measure, even when vital registration systems are in place, because deaths in this group are coded as HIV deaths, and contributory causes (such as TB) are generally not recorded [18, 19]. Nevertheless, approximately 20 % of deaths among people with HIV should be attributed to TB. People living with HIV and TB co-infection are 30 times more likely to develop active TB disease than people without HIV [19]. The occurrence of a co-infection between TB and either malaria or HIV/AIDS represents a major clinical and public health problem in low- and middle-income countries, where poverty and poor organization of health-care systems often foster the spread of those lethal, overlapping diseases [19]. In 2012 there was an estimated incidence of 1.1 million cases of HIV-positive new TB cases, 75 % of whom were living in Africa [19, 20]. At least one third of people living with HIV worldwide in 2012 were infected with TB mycobacteria, although not yet ill with active TB. Asymptomatic, subclinical TB, with negative findings on a sputum smear and chest X-ray, and positive culture results, is a common feature

of HIV-associated TB and may account for 10 % of cases in regions in which tuberculosis is endemic [21•]. Up to 25 % of patients presenting for HIV care in such regions have undiagnosed active tuberculosis. Sub-Saharan Africa has the highest rates of active TB per capita, driven primarily by the HIV epidemic [19, 22]. The persistence of TB in the setting of poor existing health infrastructure has led to an increase in drug-resistant cases, exacerbated by the HIV co-infection [23]. The continued increase in drug resistance threatens to undo decades of progress in controlling the disease and presents a growing barrier to achieving any permanent result in the fight for TB elimination [24, 25].

The problem of multidrug-resistant TB: current global issues and trends

Although the existence of multidrug-resistant strains of M. tuberculosis was known many decades ago, the description of outbreaks among HIV patients and the actual importance of horizontal transmission of strains resistant both to isoniazid and rifampicin (defined as multidrug-resistant tuberculosis or MDR-TB) was described only two decades ago [24–26]. The rise and spread of multidrug-resistant tuberculosis (MDR-TB) was identified by WHO as a major global concern just from the launch of the Stop TB strategy. Recently, WHO estimated the incidence of multidrug-resistant tuberculosis to be 450,000 in 2012, ranging from 300,000 to 600,000 new patients [26]. The mortality attributed to multidrug-resistant tuberculosis was equivalent to 170,000 cases. The majority of the cases are diagnosed in eastern European and central Asian countries: it was estimated that in some countries the proportion of multidrug-resistant tuberculosis is higher than 20 % in newly treated individuals and more than 50 % in previously treated cases (Fig. 1). Multidrug-resistant TB is present in virtually all countries surveyed. More than half of these cases were in India, China, and the Russian Federation. Almost half (43.7 %) of patients with multidrug-resistant (MDR) tuberculosis in eight countries studied were resistant to at least one 2nd-line drug, and 6.7 % had extensively drug-resistant (XDR) tuberculosis, according to a study recently published in the *Lancet* [27•]. It is estimated that about 9.6 % of MDR-TB cases had XDR-TB. It is important to highlight that both MDR- and XDR-TB are a laboratory diagnosis requiring modern diagnostics available through a network of appropriate and quality-assured laboratories will have a sustainable impact on MDR-TB control. Diagnostic services for MDR-TB, including rapid TB culture and drug susceptibility testing (DST), are generally not easily accessible to patients worldwide [28]. This is because many countries only have a central lab situated in big cities with limited or no capacity to diagnose MDR-TB, leading to patient samples being referred out of the country for diagnosis. For example, before 2008, Lesotho had limited laboratory capacity and some samples of patients were referred to South Africa for diagnosis [28]. The high price of new diagnostic equipment, together with the costs of training staff and establishing new procedures inhibits several countries from taking first steps towards modernizing their laboratories. Moreover, human resources at the country level often don't have the skills required to use new diagnostic

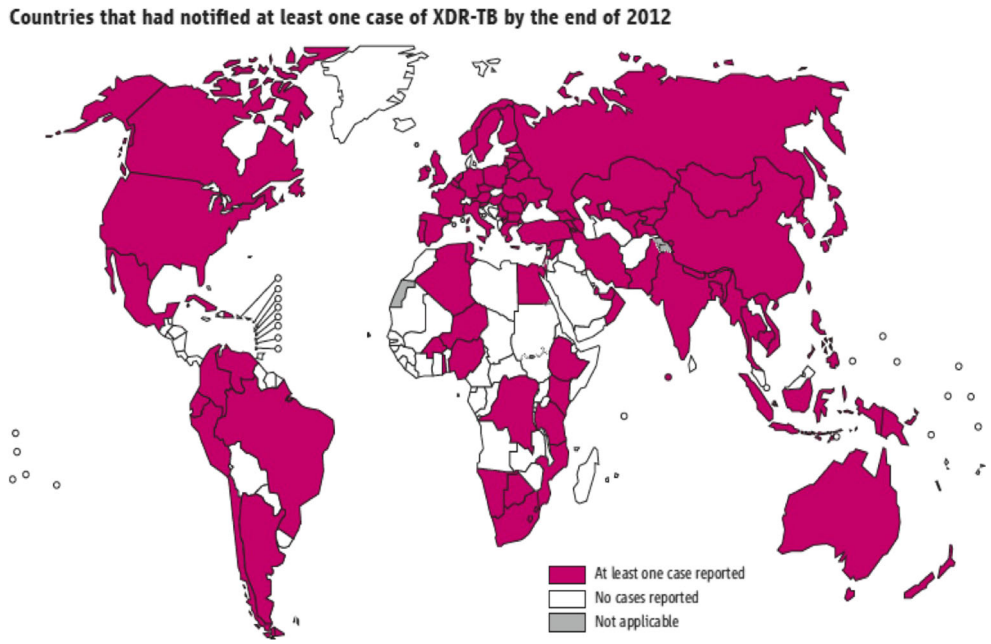

Figure 1. Worldwide diffusion of XDR-TB (source: WHO 2013[11•]).

technologies. All these problems led WHO to promote the EXPAND-TB Project for expanding the access to new diagnostics for people at risk of MDR-TB [28].

Causes and consequences of MDR-TB spread

Antibiotic resistance was described several decades ago [29]; however, recent TB surveillance data have revealed that prevalence of drug-resistant TB mycobacteria has risen to the highest rate ever recorded in history [26, 30]. The global prevalence of MDR-TB has been estimated at 3.6 % of newly diagnosed TB cases and 20.2 % of previously treated patients [30]. In Russia and other former Soviet republics, these rates rise to 20 % to 35 % for newly diagnosed cases, and 50 % to 69 % for retreatement cases [31]. The number of potentially usable anti-TB agents is significant, but the efficacy of diverse anti-TB antibiotics is not equivalent: drugs which should be administered in cases of drug-resistant TB forms are less effective, more toxic than the first-line drugs, and also more expensive [32, 33]. From a clinical perspective, the main consequence is a poor prognosis (i.e., increased mortality), poor adherence because of the adverse events, longer duration of drug exposure linked to individual and social problems [34]. The systematic analysis of multidrug-resistant cases in the community settings with regard to DOT strategy [35] found three main factors associated with the emergence of MDR- and XDR-TB: non-implementation of DOT strategy and DOT expansion strategies, insufficient supply or the poor quality of anti-tuberculosis drugs, and inadequate intake of the anti-tuberculosis medicines. The first above-mentioned condition is related to the public health system; in particular, national tuberculosis programs, which are poorly funded

and/or managed, cannot enhance the implementation or the scale-up of the DOT strategy [25]. Missing or inadequate guidelines for the therapeutic approach of tuberculosis patients, with or without a poor or missing training of health-care workers, non-standardized treatment, or missing monitoring of bacteriological evolution of the anti-tuberculosis therapy can be the basis of the emergence and spread of drug-resistant strains. Moreover, inadequate quality or quantity of anti-TB drugs managed by national tuberculosis programs, or inadequate administration of inadequate drug combinations and/or their dosages can be the background of poor drug levels: sub-inhibitory concentrations of anti-tuberculosis drugs can select the sample of drug-resistant. tuberculosis strains [30]. In most countries with high burdens of MDR-TB, the response of health systems is so far off-track that WHO's report describes it as "a crisis" [36]. Furthermore, in some countries, for instance in Belarus and China, there is an increasing rate of MDR-TB among new TB cases, demonstrating that MDR-TB strains are being actively transmitted from person to person with increasing frequency [11•, 37•]. Paradoxically, based on old data for susceptible TB, it can be argued that from a public health perspective, poor treatment programmes are worse than no TB control at all [38, 39].

Besides the health system-related factors, patient-related variables can be considered: side effects can decrease quality of life and, consequently, adherence to anti-tuberculosis medications; stigma for the disease can represent a factor that could reduce adherence, particularly when the symptoms improve and clinical recovery is more evident. Co-morbidities, such as those which cause dependency, as well as economic causes related to payment for the drugs or transport to the urban health centers, can decrease adherence. In some countries a crucial role can be played by the private sector, which could be a significant influence in the management of tuberculosis patients. WHO stated that only about one fifth (94,000 subjects) of the 450,000 estimated cases that developed MDR-TB in 2012 were actually bacteriologically confirmed, 10,000 of these were thanks to new molecular diagnostic techniques (i.e., Xpert MTB/RIF) [11•, 28]. Furthermore, only 77,000 patients with MDR-TB in 2012 began ad hoc treatment [36]. This left a large number of undiagnosed and untreated subjects continuing to spread MDR- and XDR-TB in the community.

The dramatic rise of XDR-TB burden

Until recently, the limited diffusion of DST to second-line drugs in most countries has made it very difficult, if not impossible, to obtain global data on the extent of XDR-TB. In 2009, the WHO EXPAND-TB Project was launched, with the goal of diagnosing more than 100,000 cases of MDR-TB through the introduction of rapid, quality-assured, WHO-endorsed diagnostic tests, targeting 27 countries that carry 40 % of the global MDR-TB burden [28]. Thanks to the EXPAND-TB Project, in a few years MDR-TB detection tripled in 27 Countries (namely Azerbaijan, Bangladesh, Belarus, Cameroon, Cote d'Ivoire, Djibouti, Ethiopia, Indonesia, Georgia, Haiti, India, Kazakhstan, Kenya, the Kyrgyz Republic, Mozambique, Myanmar, Lesotho, the Republic of Moldova, Peru, Rwanda, Senegal, Swaziland, Tajikistan, the United Republic of Tanzania, Uganda, Uzbekistan and Viet Nam). In 2012, nearly 30 % of the confirmed MDR-TB cases globally were diagnosed with EXPAND-TB project

support. Between 2011 and 2012, the number of MDR-TB cases detected globally increased by almost half [28]. Between 2009 and 2013, nearly 72,000 people with MDR-TB were detected through EXPAND-TB in 27 low- and middle-income countries. This project improved not only the detection rate of XDR-TB, but also its estimation. WHO estimated that almost 8,100 XDR-TB cases emerged worldwide in 2010 [39]. To date, approximately 10 % of the total MDR-TB cases are classified as XDR-TB (extensively drug-resistant tuberculosis, i.e. MDR-TB with additional resistances to any fluoroquinolones and to at least one 2nd-line injectable anti-tuberculosis drug - amikacin, capreomycin, or kanamycin) [30, 39]. In 2013, 92 countries notified at least one XDR-TB case [11•, 40, 41]. In Europe the vast majority of reported XDR-TB cases reported occurred in the eastern part of the region. Of the 3,448 MDR-TB cases tested for SLD resistance in 2011, 381 (11.0 %) were XDR [42, 43•]. The prevalence of MDR-TB among new cases globally was <5 % in all European countries, but it rose dramatically in some eastern countries, like Belarus (52.6 %), Republic of Moldova (42.0 %), and Uzbekistan (62.5 %) [42, 43•]. Fifteen of the 27 countries with high MDR-TB burden worldwide are in the European region [42, 43•]. The XDR-TB epidemic in the eastern part of the European region coincides with an increasing HIV prevalence; HIV co-infection among TB cases increased from 3.6 % in 2008 to 6.2 % in 2011 [42]. However, only 48 % of those individuals with MDR-TB exposed to anti-tuberculosis drugs were successfully treated. Moreover, only 34 out of 107 countries reached a treatment success rate of at least 75 %. Because of the limited responsiveness of XDR-TB to available antibiotics, mortality rates among patients with XDR-TB are similar to those of TB patients in the pre-antibiotic era [39]. Poor treatment outcomes were frequently high, particularly the death rate and the loss to follow-up [11•]. In the United States, the cost of hospitalization from one patient with XDR-TB is estimated to average $483,00, approximately twice the cost for MDR-TB patients. To determine the prevalence of XDR-TB in eight countries (namely Estonia, Latvia, Peru, Philippines, Russia, South Africa, South Korea, and Thailand), Dalton et al. [27•] tested sputum cultures from 1,278 adults with MDR-TB for susceptibility to 11 first-line and second-line anti-TB drugs. The investigators also used the data to identify risk factors associated with resistance to second-line drugs among people with MDR-TB. Most (70.6 %) of the patients reported one or two previous tuberculosis episodes. Nearly all of the patients in the study (92.8 %) had received first-line anti-TB drugs before enrollment, but only 195 (15.3 %) had received second-line drugs. The rate of second-line drug administration ranged from 2.7 % in South Africa to 53.5 % in South Korea. There was substantial variation in the prevalence of resistance between countries. Of the 1,278 isolates, 625 (49.0 %) were resistant to ethambutol and streptomycin in addition to isoniazid and rifampicin. Almost half (43.7 %) of the patients were resistant to at least one 2nd-line drug, with country-specific rates ranging from 33.3 % in Thailand to 62.0 % in Latvia. The overall prevalence of fluoroquinolone resistance was 12.9 %; the lowest country-specific rate was in the Philippines (7.1 %) and the highest rate was in South Korea (32.3 %).

Overall, the prevalence of resistance to at least one 2nd-line injectable drug was 20.0 %, with the lowest prevalence found in the Philippines (2.0 %) and the highest in Latvia (47.0 %). The Eastern Cape province of South Africa had a significantly higher prevalence of resistance to all three 2nd-line injectable drugs

than the other South African provinces (65 [48.9 %] of 133 vs. 10 [6.3 %] of 160 patients; $P<0.0001$). All countries had resistance to other oral second-line drugs, with an aggregate prevalence of 27.1 % (range, 13.0 - 38.0 %). Of 1,278 patients overall, XDR-TB was found in 86 (6.7 %); the prevalence of XDR tuberculosis was lowest in the Philippines and highest in South Korea. According to the estimated data from the World Health Organization, 5.4 % of patients with MDR-TB studied by Dalton et al. [27•] had XDR-TB. Prior treatment with second-line drugs increased the risk for XDR tuberculosis more than fourfold.

Risk factors for XDR-TB

Drug-resistant tuberculosis generally arises through the selection of mutated strains by inadequate therapy [39].

Thus, the most powerful predictor of the presence of MDR-TB is a history of treatment of TB [27•]. Shortage of drugs has been one of the most common reasons for the inadequacy of the initial anti-TB regimen, especially in resource-poor settings. Other major issues significantly contributing to the higher complexity of the treatment of MDR-TB is the increased cost of treatment. Other factors also play important roles in the development of MDR-TB such as poor administrative control on purchase and distribution of the drugs with no proper mechanism on quality control and bioavailability tests. Tuberculosis control programs implemented in past have also partially contributed to the development of drug resistance due to poor follow-up and infrastructure. The association between TB and poverty has been known for centuries and has a rather significant inverse association with MDR-TB. Various treatment strategies have been employed, including the use of standardised treatment regimens based upon representative local susceptibility patterns, empirical treatment based upon previous treatment history and local drug susceptibility test (DST) patterns, and individualised treatment designed on the basis of individual DST results. Treatment outcomes among MDR-TB cases have varied widely; a recent survey of five Green Line Committee (GLC)-approved sites in resource-limited countries found treatment success rates of 70 % [41]. Treatment continues to be limited in the resource-poor countries where the demand is high. The ultimate strategy to control multidrug-resistant tuberculosis is one that implements a comprehensive approach incorporating treatment of multidrug-resistant tuberculosis based upon principles closely related to those of its general DOTS (DOT, short-course) strategy for TB control: sustained political commitment; a rational case-finding strategy including accurate, timely diagnosis through quality-assured culture and DST; appropriate treatment strategies that use second-line drugs under proper case management conditions; uninterrupted supply of quality-assured antituberculosis drugs; standardised recording and reporting system. Substantially, previous treatment with second-line drugs was consistently the strongest risk factor for resistance to these drugs, which increased the risk of XDR tuberculosis by more than four times [27•]. Fluoroquinolone resistance and XDR tuberculosis were more frequent in women than in men. Unemployment, alcohol abuse, and

smoking were associated with resistance to second-line injectable drugs across countries. Other risk factors differed between drugs and countries.

Consequences for health policy of XDR-TB

The issue of drug resistance is not associated with only one variable, and the public health solution should be comprehensive, including numerous stakeholders. XDR-TB diagnosis is established by laboratory methods. It needs adequate microbiologic settings, tools, knowledge, and expertise to achieve a proper recognition of antibiotic sensitivity (DST). Accurate, reliable, and prompt TB laboratory services should be coordinated fully with the provider and public health professionals caring for persons with TB [45]. Test results must be available in a time frame to make prompt decisions for proper management. The World Health Organization recognized XDR-TB as a major challenge to be addressed as part of the Stop TB strategy, launched in 2006 [39, 41, 44]. In April 2009, WHO convened a ministerial meeting of countries with a high burden of MDR-TB in Beijing, China, paving the way in May 2009 for the 62nd World Health Assembly to adopt resolution WHA62.15 on prevention and control of MDR-TB and XDR-TB, urging member states to take action on multiple fronts towards achieving universal access to diagnosis and treatment of MDR-/XDR-TB by 2015. National programmes should investigate wider social determinants of drug-resistant tuberculosis, and establish locally tailored solutions including direct observation of treatment, socio-economic support, and a patient-centred approach to care [46]. National TB control programmes working with all health services can prevent XDR-TB by ensuring that all practitioners working with people with TB adhere to the International Standards for TB Care. These emphasize providing proper diagnosis and treatment to all TB patients, including those with drug-resistant TB; assuring regular, timely supplies of all anti-TB drugs; proper management of anti-TB drugs and providing support to patients to maximize adherence to prescribed regimens; caring for MDR/XDR-TB cases in services with proper ventilation, and minimizing contact with other patients, particularly those with HIV, especially in the early stages before treatment has had a chance to reduce the infectiousness. The emergence and growth of highly resistant strains of tuberculosis make the development of new drugs and rapid diagnostics for tuberculosis—and increased funding to strengthen global control efforts, research, and advocacy—a dramatically pressing issue [47•]. In confronting the challenge presented by XDR-TB, one immediate priority is to build community and palliative treatment care facilities at national and regional levels, and to adapt existing structures in order to prevent the continued transmission of XDR-TB within hospitals and the community by untreatable or dying patients with XDR-TB or by patients for whom treatment has failed [48]. To protect health-care workers who may come into contact with infectious TB patients, appropriate and strict infection control measures must be implemented in health-care facilities at all times. Health-care workers are also encouraged to make sure that

they are aware of their HIV status so that they can restrict putting themselves at risk for exposure.

Principles of treatment of XDR-TB

- Construction of a treatment regimen for extensively drug-resistant tuberculosis (XDR-TB) is extremely challenging. However, the principles of treatment for XDR-TB are the same of MDR-TB. The treatment with currently available anti-TB therapies to achieve relapse-free cure is long (up to 2 years) and undermined by a high frequency of adverse drug events, suboptimal treatment adherence, high costs, and low treatment success rates.
- The number of drugs in a multidrug regimen and the total treatment duration depend on the bactericidal and sterilizing activities of the TB drugs included [49].
- Drugs not previously used by the patient or those with in vitro activity based on drug susceptibility testing (DST) results are more likely to be effective. For this reason, a detailed drug history is important for formulating the XDR-TB regimen. Where available, drug concentration monitoring can be used to optimize drug exposure, thereby contributing to effective and safe TB treatment.
- Treatment of XDR-T should be reserved to specialized centers, and patients must be often hospitalized for long periods, in isolation.

Pharmacologic treatment: general principles

- Regimens should be composed of at least six drugs in the intensive phase and four in the continuation phase [50••]. Treatment should be based, when possible, on proven or probable susceptibility to at least four drugs [51].
- WHO has recommended a standardized treatment regimen that consists of at least four drugs that are known or likely to be effective against the drug-resistant M. tuberculosis strain harboured by the patient, plus any first-line oral drug according to DST results, namely ethambutol and pyrazinamide. However, these drugs should not be counted among the minimum of four active drugs [43•].
- The selection of drugs to be added should follow a hierarchical approach according to their expected activity. A meta-analysis provides empiric evidence that the use of later-generation fluoroquinolones significantly improved treatment outcomes in patients with XDR-TB, even though DST demonstrated resistance to a representative fluoroquinolone [47•]. Bacillary resistance to fluoroquinolones clearly influences the prognosis in XDR-TB.

- While data on efficacy and safety are limited, the incorporation of bedaquiline into regimens designed to treat XDR-TB may be considered [49]. Bedaquiline is unquestionably a promising diarylquinoline, which inhibits the proton pump ATP synthase of M. tuberculosis as an add-on to a MDR-TB backbone treatment regimen and showed significant improvement in the rate of culture conversion by 2 months [52].
- Then consider injectable second-line drugs (amikacin, kanamycin, or capreomycin) which should be continued for at least 6 months after culture conversion, and every other active second-line drug such as prothionamide, ethionamide, cycloserine, terizidone, and p-aminosalicylic acid. In cases of total fluoroquinolone-resistance, group 5 drugs, according to the WHO classification, notably linezolid [53], and possibly high-dose isoniazid (to be considered when the drug resistance is related to a mutation in the inhA gene of M. tuberculosis) and clofazimine, are often required to optimise treatment outcomes.
- Recently, a combination of meropenem/clavulanic acid was explored for the treatment of patients with XDR-TB and it may be considered more effective than clarithromycin or amoxicillin/clavulanic acid. The optimal duration of XDR-TB therapy is controversial, due to lack of evidence. WHO has recommended a treatment duration of 18 – 24 months or longer [50••].

Class of drugs: aminoglycosides

Amikacyn

Standard dosage	Adults: 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 g); 15 mg/kg/dose, three times per week can be used after culture conversion is documented after initial period of daily administration. >59 years of age: 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose three times per week. Children: 15–30 mg/kg/day (max 1 g) 5–7 days per week. 15–30 mg/kg/day (max 1 g) three days per week after initial period daily.
Contraindications	Pregnancy — relative contraindication (congenital deafness). Hypersensitivity to aminoglycosides. Caution with renal, hepatic, vestibular, or auditory impairment
Main drug interactions	Co-administration of loop diuretics (furosemide) and aminoglycoside antibiotics carries an increased risk of ototoxicity.
Main side effects	Common: Local pain with intramuscular injections. Proteinuria. Occasional: Nephrotoxicity, ototoxicity (hearing loss), vestibular toxicity (vertigo, ataxia, dizziness). All increase with advanced age and prolonged use. Electrolyte abnormalities, including hypokalaemia, hypocalcaemia, and hypomagnesaemia. Rare: Neuropathy, rash.
Cost/cost-effectiveness	inexpensive

Class of drugs: aminoglycosides

Kanamicyn

Standard dosage	Adults: 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 g, but a large, well-built person could receive more and should have concentrations monitored). >59 years of age: 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose three times per week. Children: 15–30 mg/kg/day (max 1 g) 5–7 days per week. 15–30 mg/kg/day (max 1 g) three days per week after initial period daily. Renal failure/dialysis: 12–15 mg/kg/dose, three times weekly. Markedly obese individuals should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. For dosing, use adjusted weight as follows: Ideal body weight+40 % of excess weight. Ideal body weight (men): 50 kg plus 2.3 kg/in. over 5 ft. Ideal body weight (women): 45 kg plus 2.3 kg/in. over 5 ft. If possible, concentrations should be followed closely.
Contraindications	Pregnancy — relative contraindication (congenital deafness). Hypersensitivity to aminoglycosides. Caution with renal, hepatic, vestibular or auditory impairment
Main drug interactions	Co-administration of loop diuretics (furosemide) and aminoglycoside antibiotics carries an increased risk of ototoxicity.
Main side effects	Nephrotoxicity: Appears to be more nephrotoxic than streptomycin. Ototoxicity (hearing loss) and vestibular toxicity: Increases with advanced age and prolonged use; appears to occur slightly more commonly with kanamycin than with streptomycin and about the same frequency as amikacin. Kanamycin seems to have slightly less vestibular toxicity.
Cost/cost-effectiveness	inexpensive

Class of drugs: aminoglycosides

Streptomicyn

Standard dosage	Adults: 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 g). >59 years of age: 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose three times per week. Children: 20–40 mg/kg/day (max 1 g), 5–7 days per week. Renal failure/dialysis: 12–15 mg/kg/dose, 2-3 times weekly (not daily). Markedly obese individuals should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. For dosing, use adjusted weight as follows: Ideal body weight+40 % of excess weight. Ideal body weight (men): 50 kg plus 2.3 kg/in. over 5 ft. Ideal body weight (women): 45 kg plus 2.3 kg/in. over 5 ft.

	If possible, concentrations should be followed closely.
Contraindications	Pregnancy (congenital deafness seen with streptomycin and kanamycin use during pregnancy) Hypersensitivity to aminoglycosides; caution with renal, vestibular, or auditory impairment.
Main drug interactions	Co-administration of loop diuretics (furosemide) and aminoglycoside antibiotics carries an increased risk of ototoxicity.
Main side effects	Nephrotoxicity: Less nephrotoxic than amikacin. Ototoxicity (hearing loss): Increased with advanced age and prolonged use. Vestibular toxicity. Local pain with IM injections. Electrolyte abnormalities, including hypokalaemia, hypocalcaemia, and hypomagnesaemia.
Cost/cost-effectiveness	inexpensive

Class of drugs: penicillin/beta-lactam inhibitors

Amoxicillin/Clavunalate

Standard dosage	Expressed in amoxicillin component. Adult (and child >30 kg): 80 mg/kg/day in two divided doses Child under 30 kg: 80 mg/kg/day in two divided doses Maximum dose: 3,000 mg daily
Contraindications	Penicillin allergy; use with caution with cephalosporin allergies.
Main drug interactions	non-significant ones.
Main side effects	Common: Diarrhoea and abdominal discomfort are most common. Nausea and vomiting. Uncommon: Hypersensitivity and rash. Rare side effects have been reported in other organ systems.
Cost/cost-effectiveness	inexpensive

Class of drugs: carbapenem

Meropenem

Standard dosage	Adults: No oral absorption. Recent case–controlled study used 1,000 mg IV every 8 h. Must be given with clavulanate (available as amoxicillin/clavulanate), 125 mg every 8–12 h. Children: Not established for TB; however, for other bacterial infections in children: 20 mg/kg/dose and 40 mg/kg/dose for meningitis or particularly severe infections. Given IV every 8 h up to 2 g per dose. Renal failure/dialysis: Adjustment required – 750 mg every 12 h for creatinine clearance of 20–40 ml/min; 500 mg every 12 h for creatinine clearance <20 ml/min.
Contraindications	Carbapenem intolerance
Main drug interactions	non-significant

Main side effects	Diarrhoea, nausea or vomiting. Seizure (noted with CNS infection), but rare compared to imipenem. Rarely elevated LFTs, haematologic toxicity, hypersensitivity
Cost/cost-effectiveness	expensive

Class of drugs: carbapenem

Imipenem/Cilastin

Standard dosage	Adults: 1,000 mg IV every 12 h. (dosed on the imipenem component). Should be given with clavulanate (available as amoxicillin/clavulanate) 125 mg every 8–12 h. Children: Meropenem preferred. See Meropenem drug sheet for dosing.
Contraindications	Carbapenem intolerance; meningitis (use meropenem rather than imipenem).
Main drug interactions	ganciclovir
Main side effects	Common: Diarrhoea, nausea, or vomiting. Less common: Seizure (noted with CNS infection), palpitations, pseudomembranous colitis.
Cost/cost-effectiveness	expensive

Class of drugs: oxazolidonones

Linezolid

Standard dosage	Adults: 600 mg, once daily. (Reduce to 400–300 mg/day if serious adverse effects develop). Children: 10 mg/kg three times daily in children up to 11 years of age and 10 mg/kg (maximum dose 600 mg) twice daily in older children. 10 mg/kg/dose every 12 h. Vitamin B6: All patients should receive vitamin B6 while receiving linezolid.
Contraindications	Hypersensitivity to oxazolidinones. Symptoms of neuropathy (pain, numbness, tingling, or weakness in the extremities).
Main drug interactions	Avoid use with patients taking serotonergic agents, such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine), lithium, tricyclic antidepressants, as it may cause serious CNS reactions such as serotonin syndrome.
Main side effects	Myelosuppression (decreased level of platelets, decreased level of white blood cells, and/or anaemia). Diarrhoea and nausea. Optic and peripheral neuropathy may be irreversible and linezolid should stopped if these develop; weigh against the risk of permanent blindness or disabling permanent neuropathy. Lactic acidosis – patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving linezolid should receive immediate medical evaluation, including a lactic acid blood test.
Cost/cost-effectiveness	expensive

Class of drugs: carbothionamide group, derivatives of isonicotinic acid

Ethionamide/Protionamide

Standard dosage Adults: 15–20 mg/kg/day frequently divided (max dose 1 g per day); usually 500–750 mg per day in two divided doses or a single daily dose.
Children: 15–20 mg/kg/day usually divided into 2–3 doses (max dose 1 g per day). A single daily dose can sometimes be given at bedtime or with the main meal. Many individuals require gradual ramping up of the dose and treatment for gastrointestinal upset.
Pyridoxine (vitamin B6): Although there is little supporting data, most MDR-TB experts recommend that all patients should receive vitamin B6 while taking ethionamide. Suggested dose for adults is 100 mg and children should receive a dose proportionate to their weight (1–2 mg/kg/day, with a usual range of 10–50 mg/day).
Renal failure/dialysis: No change.

Contraindications Sensitivity to ethionamide.

Main drug interactions Cycloserine may exaggerate adverse effects

Main side effects Gastrointestinal upset and anorexia: sometimes intolerable (symptoms are moderated by food or taking at bedtime). Premedication with an antiemetic like ondansetron is often helpful. Low-dose ativan 0.5 mg has also been used successfully. Metallic taste. Hepatotoxicity.
Endocrine effects: Gynaecomastia, hair loss, acne, impotence, menstrual irregularity, and reversible hypothyroidism – treat with thyroid replacement.
Neurotoxicity (patients taking ethionamide should take high doses of vitamin B6). Side effects may be exaggerated in patients also taking cycloserine.

Cost/cost-effectiveness expensive

Class of drugs: diarylquinoline

Bedaquiline

Standard dosage Adults: 400 mg once daily for 2 weeks, followed by 200 mg three times per week for 22 weeks with food.
Children: Not yet determined.
If a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose, but should continue the usual dosing schedule. From week 3 onwards, if a 200-mg dose is missed, patients should take the missed dose as soon as possible, and then resume the regimen of three times a week.

Contraindications Do not use or discontinue bedaquiline if:

- Clinically significant ventricular arrhythmia.
- A QTcF interval of >500 ms (confirmed by repeat ECG).
- Severe liver disease.

Use with caution in the following situations (with more frequent ECG monitoring and evaluation of risk versus benefit):

- With other QT prolonging drugs (see drug interactions)

- A history of torsade de pointes
- A history of congenital long QT syndrome
- A history of hypothyroidism and bradyarrhythmias
- A history of uncompensated heart failure
- Serum calcium, magnesium, or potassium levels below the lower limits of normal.

Main drug interactions Bedaquiline is metabolized by CYP3A4. Rifampicin (a CYP3A4 inducer) reduces bedaquiline in blood by half. Efavirenz based on a single-dose study appears to reduce the amount of bedaquiline though inducing CYP3A4. CYP3A4 inhibitors (e.g. azole anti-fungal drugs, some macrolides, protease inhibitors, and many others) can raise the level of bedaquiline but can be considered for use if the benefits outweigh the risk.
Avoid use with other drugs that prolong the QT interval as additive QT prolongation may occur (e.g. clofazimine, fluoroquinolones, delamanid, azole anti-fungal drugs, and many others); any syncopal event (fainting) should prompt an immediate medical evaluation and ECG.

Main side effects Common: Gastrointestinal distress (nausea, vomiting, abdominal pain, loss of appetite), joint pain (arthralgia), headache. (Note: haemoptysis and chest pain were also more frequently reported in the group receiving bedaquiline than in the placebo treatment group).
Less common: QT prolongation, hyperuricaemia, phospholipidosis (the accumulation of phospholipids in the body's tissues), elevated aminotransferases. Possibly an increased risk of pancreatitis.
WARNINGS: A significant imbalance in fatalities was noted in Trial C208 Stage 2, with a higher number of deaths in the bedaquiline group (10 vs. two in the placebo group; RR=5.1; $p=0.017$). There was no sudden death reported in the study. There was no discernible pattern for cause of deaths and the reason for the imbalance in deaths is not clear.

Cost/cost-effectiveness expensive

Class of drugs: cyclic polypeptide

Capreomycin

Standard dosage Adults: 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 g, but a large, muscular person could receive more and should have the concentrations monitored); 15 mg/kg/dose, 2–3 times per week after an initial period of daily administration (some experts use up to 25 mg/kg/dose for intermittent therapy; monitor concentrations). In persons >59 years of age: 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after the initial period. Alternatively, 15 mg/kg/dose, three times per week.
Children: 15–30 mg/kg/day (max 1 g), 5–7 days per week. 130 mg/kg/day (max 1 g), 2–3 days per week after initial period daily.
Renal failure/dialysis: 12–15 mg/kg/dose, 2–3 times weekly (not daily). Markedly obese individuals should have an adjusted dose due to decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. For dosing, use adjusted weight as follows: Ideal body weight+40 % of

	excess weight. Ideal body weight (men): 50 kg plus 2.3 kg/ in. over 5 ft. Ideal body weight (women): 45 kg plus 2.3 kg/in. over 5 ft. Serum concentrations should be followed closely when possible.
Contraindications	Hypersensitivity to capreomycin. Some experts would not use capreomycin if vestibular side effects resulted from aminoglycoside use. Generally avoided during pregnancy due to congenital deafness seen with aminoglycosides and mechanism of ototoxicity may be similar with capreomycin. There are case reports of its safe use during pregnancy (unaffected newborns).
Main side effects	Similar to the aminoglycosides. Nephrotoxicity: 20–25 % including proteinuria, reduced creatinine clearance, and depletion of potassium and magnesium. Ototoxicity (hearing loss): Occurs more often among the elderly or those with pre-existing renal impairment and vestibular toxicity. Local pain with intramuscular injections. Electrolyte abnormalities, including hypokalaemia, hypocalcaemia and hypomagnesaemia.
Cost/cost-effectiveness	expensive

Class of drugs: Macrolides

Clarithromycin

Standard dosage	Adults: 500 mg twice daily or 1 g daily of extended release formulation. Children: 7.5 mg/kg q 12 h up to 500 mg. Renal failure/dialysis: The drug is cleared both hepatically and renally. In severe renal impairment, the interval doses should be increased, i.e. 500 mg/day.
Contraindications	Patients with known hypersensitivity to macrolide antibiotics. Should not be given with the any of the following drugs: bedaquiline, cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine.
Main drug interactions	bedaquiline, cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine.
Main side effects	Common: Diarrhoea, nausea, abnormal taste, dyspepsia, abdominal pain / discomfort, headache. Rare allergic skin reactions, liver toxicity, QT prolongation, clostridium difficile colitis, hearing loss.
Cost/cost-effectiveness	inexpensive

Class of drugs: iminophenazine

Clofazimine

Standard dosage	Adults: 100–200 mg daily (oral) has been used. A regimen of 200 mg daily for 2 months, followed by 100 mg daily has been used. Children: Limited data, but doses of 1 mg/kg/day have been given.
Contraindications	Allergy to clofazimine.

Main drug interactions	Using with drugs that prolong the QT interval may cause additive QT prolongation (e.g. bedaquiline, fluoroquinolones, delamanid, azole anti-fungal drugs, and many others); further research is needed to understand potential interactions with antiretrovirals.
Main side effects	Common: Orange/red discoloration of skin, conjunctiva, cornea and body fluids. Dry skin, pruritus, rash, ichthyosis, xerosis. Gastrointestinal intolerance. Photosensitivity. Less common: retinopathy, severe abdominal symptoms, bleeding and bowel obstruction; QT prolongation.
Cost/cost-effectiveness	expensive

Class of drugs: analog of D-alanine

Cycloserine and Terizidone

Standard dosage	Adults: 10–15 mg/kg/day usually (max. 1000 mg/day); Usually 500–750 mg/day given in two divided doses or once a day if tolerated. Some patients may require only alternate day 250 mg and 500 mg dosing to avoid toxicity. Children: 10–20 mg/kg/day divided every 12 h (daily maximum 1 g). Pyridoxine (vitamin B6): Although supporting data are not extensive, MDR-TB experts recommend that all patients should receive vitamin B6 while taking cycloserine. Adults need 100 mg or more (or 50 mg per 250 mg of cycloserine) and children should receive a dose proportionate to their weight (1–2 mg/kg/day, with an usual range of 10–50 mg/day). Renal failure/dialysis: 250 mg once daily or 500 mg, three times per week; monitor drug concentrations to keep peak concentrations <35 mcg/ml.
Contraindications	Relative contraindications include seizure disorder, psychotic disease, or alcohol abuse.
Main drug interactions	Alcohol.
Main side effects	CNS toxicity, including inability to concentrate and lethargy. More serious CNS side effects, including seizure, depression, psychosis and suicidal ideation, usually occur at peak concentrations >35 mcg/ml, but may be seen in the normal therapeutic range. Other side effects include peripheral neuropathy and skin changes. Skin problems include lichenoid eruptions and Stevens-Johnson syndrome.
Cost/cost-effectiveness	expensive

Class of drugs: fluorquinolones

Gatifloxacin

Standard dosage	400 mg/day
Contraindications	Pregnancy Intolerance of fluoroquinolones Diabetes. Gatifloxacin can worsen diabetes and glycaemic control.
Main side effects	Generally well tolerated. Occasional: gastrointestinal intolerance;

	Rare CNS-headache; malaise; insomnia; restlessness; dizziness; allergic reactions; diarrhoea; photosensitivity; increased liver function tests; tendon rupture (increased incidence seen in older men with concurrent use of corticosteroids). Severe dysglycaemia, hypoglycaemia and hyperglycaemia, and diabetes have been reported (many countries have removed the drug form their national formularies for this reason).
Cost/cost-effectiveness	expensive

Class of drugs: fluorquinolones

Levofloxacin

Standard dosage	Adults: For treatment of TB disease 10–15 mg/kg once daily. Children: 5 years and under: 15–20 mg/kg split into two doses (morning and evening). Over 5 years: 10–15 mg/kg once daily. Renal failure/dialysis: 750–1000 mg/dose, three times weekly (not daily) for creatinine clearance <30 ml/min.
Contraindications	Fluoroquinolone intolerance, prolonged QTc, pregnancy (relative contraindication).
Main side effects	Nausea and bloating. Headache, dizziness, insomnia or tremulousness. Rare tendon rupture, arthralgias (can usually be treated symptomatically). QTc prolongation, hypoglycaemia.
Cost/cost-effectiveness	expensive

Class of drugs: fluorquinolones

Moxifloxacin

Standard dosage	Adults: 400 mg daily (oral or IV). Children: No established dose. Renal failure/dialysis: No dose adjustment required.
Contraindications	Fluoroquinolone intolerance, prolonged QTc.
Main drug interactions	do not take milk-based products, antacids (especially aluminum-coating), vitamin supplements, or sucralfate within 2 h of this medication or 4 h after.
Main side effects	Nausea and diarrhea. Headache and dizziness. Rare tendon rupture; arthralgias. Rare hepatotoxicity. QTc prolongation, hypo-/hyperglycaemia.
Cost/cost-effectiveness	expensive

Class of drugs: salicylic acid - anti-folate

Para-aminosalicylic acid (PAS)

Standard dosage	Adults: 8–12 grams per day divided 2–3 times per day Children: 200–300 mg/kg/day divided 2–4 times per day

	Renal failure/dialysis: No change
Contraindications	Pregnancy (relative).
Main drug interactions	non-significant
Main side effects	Gastrointestinal distress (less with the PASER. formulation than with older preparations) Rare hepatotoxicity and coagulopathy Reversible hypothyroidism (increased risk with concomitant use of ethionamide); treat with thyroid replacement
Cost/cost-effectiveness	expensive

Class of drugs: rifamycin

Rifapentin

Standard dosage	Adults: 600 mg once weekly during the continuation phase of treatment. (Not recommended in the US for the initial treatment phase). Higher daily doses are being studied. Children: (12 years and older), 600 mg once weekly if >45 kg; 450 mg once weekly if <45 kg.
Contraindications	History of hypersensitivity to any of the rifamycins (i.e. rifampin or rifabutin)
Main drug interactions	Dosage adjustment may be required for concurrent medications. Concurrent treatment with most antiretroviral drugs is not recommended, as antiretroviral drug concentrations are substantially reduced, as with rifampin. However, rifapentine plasma concentrations are not affected by most other drugs (based on current data).
Main side effects	Many drug interactions. Red–orange staining of body fluids Rash and pruritis Hypersensitivity reaction Hepatoxicity Haematologic abnormalities.
Cost/cost-effectiveness	expensive

Emerging therapies

- New anti-TB drugs are currently being developed and programme managers should keep abreast of WHO recommendations as they are released and updated though the website of the Task Force for New Drug Policy Development [50••]. For more information on treatment of XDR-TB and compassionate use and early access programmes see the 2014 WHO's Companion Handbook on the management of resistant TB [50••].
- New drugs that have been evaluated for the treatment of TB include delamanid (OPC-67683), PA-824, and others [5]. Of the new compounds, delamanid and PA-824 are two nitroimidazopyrans with good early bactericidal activity [54].

- With the availability of new drugs for the treatment of MDR/XDR-TB, the hierarchical order for choosing anti-TB drugs will have to be redefined and updated regularly by WHO.

Pediatric considerations

- Management of pediatric MDR/XDR-TB is difficult to assess because in children it is seriously under-reported. Through incomplete or inadequate regimens, as seen in adults, this infection in children is usually caused by the acquisition of an already-resistant strain. Therefore, the treatment is usually assessed according to the susceptibility of the index case strain since it is harder to obtain a bacteriological specimen from the child. The optimal duration of MDR/XDR-TB treatment in children is unclear but shorter regimens may suffice due to the usually more rapid bacterial clearance. Another important issue is the lack of available child-friendly preparations [55].

Surgical therapy

- The most common surgical procedure in patients with pulmonary drug-resistant TB is resection surgery (taking out part or all of a lung).
- Large case series analysis has proven resection surgery to be effective and safe under appropriate surgical conditions [56]. It is considered an adjunct to chemotherapy and appears to be beneficial for patients when skilled thoracic surgeons and excellent postoperative care are available [57].
- Surgery is not indicated in patients with extensive bilateral disease [50••].

Diet and lifestyle

- XDR-TB treatment (as with all TB treatment) and care should contain integrated nutritional assessment counseling and support for the duration of the illness.
- In addition to causing malnutrition, as in other forms of TB, XDR-TB can be exacerbated by poor nutritional status. Without nutritional support, patients, especially those already with borderline hunger, can become enmeshed in a vicious cycle of malnutrition and disease.
- The second-line anti-TB medications can also further decrease appetite, making adequate nutrition a greater challenge.
- Food support may improve treatment adherence in settings were food insecurity is an important access barriers.
- Vitamin B6 (pyridoxine) should be given to all MDR-TB patients receiving cycloserine or terizidone, and a high dosage of isoniazid or linezolid to prevent neurological side effects.

- Vitamin (especially vitamin A) and mineral supplements can be given in areas where a high proportion of the patients have these deficiencies.
- If multivitamins and minerals (zinc, iron, calcium, etc.) are given they should be dosed three to four hours apart from the fluoroquinolones, as these can interfere with the absorption of these drugs.

Compliance with Ethics Guidelines

Conflict of Interest
Marco Confalonieri declares that he has no conflict of interest.
Cristina Maurel declares that she has no conflict of interest.
Mario Santagiuliana declares that he has no conflict of interest.
Roberto Luzzati declares that he has no conflict of interest.
Cinzia Longo declares that she has no conflict of interest.
Mitja Jevnikar declares that she has no conflict of interest.
Rossella Cifaldi declares that she has no conflict of interest.
Giulia Amadio declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. WHO. WHO tuberculosis program: framework for effective tuberculosis control. Geneva: World Health Organization; 1994 (WHO/TB/94.179).
2. Dye C, Espinal MA, Watt CJ, Mbiaga C, Williams BG. Worldwide incidence of multidrug-resistant tuberculosis. J Infect Dis. 2002;185:1197–202.
3. Migliori GB, De Iaco G, Besozzi G, Centis R, Cirillo DM. First tuberculosis cases in Italy resistant to all tested drugs. Euro Surveill. 2007;12. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=3194.
4. Nathanson CM, Cuevas LE, Cunningham J, et al. The TDR tuberculosis specimen bank: a resource for diagnostic test developers. Int J Tuberc Lung Dis. 2010;14:1461–7.
5. Velayati AA, Masjedi MR, Farnia P, et al. Emergence of new forms of totally drug-resistant Tuberculosis Bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. Chest. 2009;136:420–5.
6. Udwadia ZF, Amale RA, Ajbani KK, Rodrigues C. Totally drug-resistant tuberculosis in India. J Infect Dis. 2012;54:579–81.
7. Löroth K, Raviglione M. Global epidemiology of tuberculosis: prospects for control. Semin Respir Crit Care Med. 2008;29:481–91.
8. World Health Organization. Global tuberculosis control. Geneva: World Health Organization; 2008.
9. Raviglione M. The new Stop TB Strategy and the Global Plan to Stop TB, 2006-2015. Bull World Health Organ. 2007;85:327.
10. Udwadia ZF, Amale RA, Ajbani KK, Rodrigues CS. Nomenclature of drug-resistant tuberculosis. Lancet Infect Dis. 2013;13:917.
11.• World Health Organization. Global tuberculosis report 2013. Geneva: WHO; 2013.
The most recently published WHO's global TB report: an official source of useful information and detailed data on the global and regional epidemiology of TB.

12. Hill AN, Becerra J, Castro KG. Modelling tuberculosis trends in the USA. Epidemiol Infect. 2012;140:1862–72.
13. WHO. Global tuberculosis report 2012. Geneva: World Health Organization (http://www.who.int/tb/publications/global_report/en/).
14. Lawn SD, Zumla AI. Tuberculosis. Lancet. 2011;378:57–72.
15. WHO. Surveillance report: tuberculosis surveillance and monitoring in Europe. Geneva: World Health Organization; 2012. http://ecdc.europa.eu/en/publications/Publications/1203-Annual-TB-Report.pdf.
16. Zumla A, Raviglione M, Hafner R, von Reyn CF. Tuberculosis. N Engl J Med. 2013;368:745–55.
17. Glaziou P, Falxon D, Foyd K, Raviglione M. Global epidemiology of tuberculosis. Semin Respir Crit Care Med. 2013;34:3–16.
18. World Health Organization. Global tuberculosis control 2009. Geneva: World Health Organization; 2009.
19. Joint United Nations Programme on HIV/AIDS (UNAIDS). Global report 2013. UNAIDS 2013. (http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/unaids_global_report_2013_en.pdf).
20. The South African National AIDS Council. National Strategic Plan (NSP) for HIV and AIDS, TB and STIs 2012 – 2016. SANAC 2012 (http://www.sanac.org.za/nsp/the-national-strategic-plan).
21.• Gray JM, Cohn DL. Tuberculosis and HIV coinfection. Semin Respir Crit Care Med. 2013;34:32–43. .

An interesting review covering all the aspects of HIV and TB co-infection.

22. Corbett EL, Watt CJ, Walker N, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003;163:1009–21.
23. Onozaki I, Raviglione M. Stopping tuberculosis in the 21st century: goals and strategies. Respirology. 2010;15:32–43.
24. Migliori GB, Loddenkemper R, Blasi F, Raviglione M. 125 years after Robert Koch's discovery of the tubercle bacillus: the new XDR-threat. Is "science" enough to tackle the epidemic? Eur Respir J. 2007;29:423–7.
25. Raviglione M, Marais B, Floyd K, et al. Scaling up interventions to achieve global tuberculosis control: progress and new developments. Lancet. 2012;379:1902–13.
26. World Health Organization. Towards universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis by 2015. WHO Progress Report 2011. Geneva: World Health Organization; 2011.
27.• Dalton T, Cegielski P, Akksilp S, et al. Prevalence of and risk factors for resistance to second line drugs in people with multidrug-resistant tuberculosis prospective cohort study. Lancet. 2012;380:1406–17.

This important study actively firstly investigated the actual epidemiology of XDR-TB in eight countries searching for its risk factors.

28. The Expand-TB Project. Reaching people with MDR-TB - progress in diagnosis: a key step in overcoming the MDR-TB crisis. Geneva: World Health Organization; 2014.
29. Powers JH. Antimicrobial drug development - the past, the present, and the future. Clin Microbiol Infect. 2004;10 Suppl 4:23–31.
30. Sotgiu G, Migliori GB. Facing multi-drug resistant tuberculosis. Pulm Pharmacol Ther. 2014. doi:10.1016/j.pupt.2014.04.006.
31. Ahmad S, Makaddas E. Current status and future trends in the diagnosis and treatment of drug-susceptible and multi-resistant tuberculosis. J Infect Pub Health. 2014;7:75–91. 31.

31

32. Ahuja SD, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9:e1001300.
33. Diel R, Vandeputte J, de Vries G, et al. Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. Eur Respir J. 2014;43:554–65.
34. Zumla A, Gillespie SH, Hoelscher M, et al. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. Lancet Infect Dis. 2014;14:327–40.
35. Caminero JA. Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding. Int J Tuberc Lung Dis. 2010;14:382–90.
36. Zumla A, George A, Sharma V, et al. WHO's 2013 global report on tuberculosis: successes, threats, and opportunities. Lancet. 2013;382:1765–7.
37.• Zhao Y, Xu S, Wang L, et al. National survey of drug-resistant tuberculosis in China. N Engl J Med. 2012;366:2161–70.

A recent national survey of drug-resistant TB in world most highly populated Country.

38. Chiang CY, Van Deun A, Enarson DA. A poor drug-resistant tuberculosis programme is worse than no programme: time for a change. Int J Tuberc Lung Dis. 2013;17:714–8.
39. Günther G. Multidrug-resistant and extensively drug-resistant tuberculosis: current concepts and future challenges. Clin Med. 2014;14:279–85.
40. Migliori GB, Besozzi G, Girardi E, et al. Clinical and operational value of the extensively drug-resistant tuberculosis definition. Eur Respir J. 2007;30:623–6.
41. Sotgiu G, Ferrara G, Matteelli A, et al. Epidemiology and clinical management of XDR-TB: a systematic review by TBNET. Eur Respir J. 2009;33:871–81.
42. European Centre for Disease Prevention and Control, WHO Regional Office for Europe. Tuberculosis

surveillance and monitoring in Europe. Stockholm: European Centre for Disease Prevention and Control; 2013.

43.• Lange C, Abubakar I, Jan-Willem C, et al. Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement. Eur Respir J. 2014;44:23–63.

An updated consensus statement on MDR-TB and XDR from an European perspective.

44. World Health Organization. The global MDR-TB and XDR-TB response plan 2007-2008. Geneva: WHO; 2007. Publication no. WHO/HTN/TB/2007.387.

45. LoBue P, Sizemore C, Castro KG. Plan to combat extensively drug-resistant tuberculosis recommendations of the Federal Tuberculosis Task Force. MMWR. 2009;58(RR03):1–43.

46. Abubakar I, Zignol M, Falzon D, et al. Drug-resistant tuberculosis: time for visionary political leadership. Lancet Infect Dis. 2013;13:529–39.

47.• Dheda K, Gumbo T, Gandhi NR, et al. Global control of tuberculosis: from extensively drug-resistant to untreatable tuberculosis. Lancet Respir Med. 2014;2:321–38.

A recent comprehensive review on XDR-TB providing documented epidemiolocial data and interesting practical suggestions for health systems policies.

48. Dheda K, Migliori GB. The global rise of extensively drug-resistant tuberculosis: is the time to bring back sanatoria now overdue? Lancet. 2012;379:773–5.

49. Caminero JA, Matteelli A, Lange C. Treatment of TB. In: Lange C, Migliori GB, eds. Tuberculosis. Eur Respir Monogr 2012;58:154–166.

50.•• World Health Organization. The Companion Handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: WHO Document Production Services; 2014.

Authoritative, clear and updated handbook by WHO, fully dedicated to resistant-TB management. To be consulted daily for everyone who care for patients with XDR-TB.

51. Keertan et al. Global control of tuberculosis: from extensively drug-resistant to untreatable tuberculosis. Lancet Respir Med. 2014;2:321–38.

52. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med. 2009;360:2397–405.

53. Chang KC, Yew WW, Tam CM, et al. WHO group 5 drugs and difficult multidrug-resistant tuberculosis: a systematic review with cohort analysis and meta-analysis. Antimicrob Agents Chemother. 2013;57:4097–104.

54. Grosset JH, Singer TG, Bishai WR. New drugs for the treatment of tuberculosis: hope and reality. Int J Tuberc Lung Dis. 2012;16:1005–14.

55. Ettehad D, Schaaf HS, Seddon JA, Cooke GS, Ford N. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2012;12:449–56.

56. Francis RS, Curwen MP. Major surgery for pulmonary tuberculosis: final report. Tubercle. 1964;45(Suppl):5–79.

57. WHO. Emergence of Mycobacterium tuberculosis with extensive resistance to second-line drugs – worldwide, 2000–2004. MMWR. 2006;55:301–5.