TB is probably one of the most long-standing and harmful diseases in human history [1]. In the 1950s, a cure was possible for the majority of patients through a combination of drugs [2]. However, the uncontrolled use of anti-TB drugs through the following 50 years has resulted in the escalation of *Mycobacterium tuberculosis* strains that are drug resistant (DR). As a result, TB in certain patients has cure rates similar to those of the pre-antibiotic era.

Initial resistance was to streptomycin (SM) and para-aminosalicylic acid (PAS), the first anti-TB drugs [3]. Subsequently, strains resistant to isoniazid (INH) and especially, strains with INH resistance linked to SM and PAS resistance, appeared, which were the three TB treatment bases. Certain TB cases started to be referred to as 'incurable'. Studies with different drug combinations were performed in an attempt to cure such patients [4].

Rifampicin (RMP), the most powerful anti-TB drug up until the present day, was developed in 1963. Its generalized and sometimes improper use during the late 1960s and 1970s furthered the development of resistant strains. Even more dangerous was the development of strains resistant to both RMP and INH, the most potent and effective anti-TB drugs [2,4]. These strains were defined as multidrug-resistant TB (MDR-TB). Despite the large benefits of the directly observed treatment short-course (DOTS) strategy, which was introduced worldwide in 1992, concerns about incurable TB grew during the 1990s. During this last decade, the management of MDR-TB cases has been an international priority, as a result of approximately 500,000 estimated new cases each year [5]. There are world regions where the situation is particularly severe, such as the former Soviet Union Republics [6].

Despite some progress in the control of MDR-TB [4] and the development of an international approach for treating the disease, even more severe forms of TB, extensively drug-resistant TB (XDR-TB) [7–9] and totally drug-resistant TB (TDR-TB), have evolved [10]. Drug resistance is thus putting previous progress in the development of TB treatment at risk, and accordingly demands new practices and
approaches. In addition, HIV is fuelling the epidemic, creating fatal nosocomial outbreaks [9]. The old TB is again highly lethal in many regions.

Consistent evidence for the appropriate management of DR-TB does not exist, given that the vast majority of patients during the 1960s, 1970s, 1980s and 1990s were treated as individual cases in reference centers in developed countries. Data are limited and almost nonexistent in relation to crucial aspects, such as treatment, while there are no randomized controlled trials (RCTs) evaluating different drug combinations. Management of these patients is particularly challenging since it is based on experts’ opinions, which are occasionally controversial [4]. Basic agreements on which to base standardized treatments for MDR-TB are only a recent achievement [11]. However, many issues remain where intensive research is needed to optimize diagnosis and treatment.

Within this perspective, we seek to review the current knowledge on MDR/XDR-TB and the fundamental consensus. In addition, we present a critical view of the most controversial issues, as well as a speculative 5-year future prediction of the MDR/XDR epidemic. To conclude, the authors provide their opinions on potential interventions of the most pressing concerns in the control of the epidemic.

Resistance origins: the bacteriological rationale of TB treatment
The prognosis of TB patients changed significantly approximately 60 years ago with the onset of chemotherapy. Although PAS was the first drug investigated [3], studies with SM were much more prominent during the 1940s and 1950s. These investigations became crucial in the development of the bacteriological bases for TB treatment. Shortly after the description of SM, clinical trials using it as a monotherapy were conducted in the UK [12] and the USA [13]. The case fatality was reported to be considerably reduced. However, it was also observed that patients improved over the first few months and subsequently deteriorated in many cases, due to the development of SM resistance. SM trials had a considerable impact on research for the next 20 years, which predominantly focused on methods for preventing the emergence of drug resistance. Further studies demonstrated that the addition of PAS to SM significantly lowered the risk of acquiring resistance [14].

The subsequent discovery of INH and its addition to the regimen including PAS and SM in the 1950s resulted in a highly effective regimen that was able to cure the great majority of TB patients [15]. It was around this time that the ‘bacillary populations theory’ was rationalized [16]. Since then it is commonly accepted that, of the total bacilli load, there are a number that can remain metabolically inactive (dormant) over a period of years. Eventually, these would become active again, resulting in disease (relapse). These forms are difficult to kill and require long-term treatments to sterilize the lesions. At the same time, metabolically active bacilli are responsible for the disease symptoms and also the development of resistance. TB resistance appears by selection of natural mutant strains after a drug selective pressure driven mainly by monotherapy (inappropriate prescription) or suboptimal adherence to the treatment protocol [17]. In the overall bacillary load held by a patient (from 10^6 up to 10^9 bacilli), the number of natural mutant resistant bacilli to a single drug is very low (just one or two bacilli on average). However, if these few natural mutants are selected by one or both of the previous mechanisms, they would expand into a full monoresistant population. In the case of being exposed again to a different single drug, new mutants would be selected over the previously resistant and so forth. To avoid drug resistance appearance and amplification, TB needs to be treated with several drugs concurrently. Not infrequently, monotherapy and amplification is expressed clinically as the addition of a single drug to a failing regimen [17].

Since the mid 1950s, TB has been considered a curable disease in almost all cases, with low treatment side effects. Furthermore, these reactions were significantly reduced after the discovery of ethambutol (EMB) and its addition to the regimens instead of PAS [18]. However, EMB neither increased the efficacy of the treatment schedule nor shortened its length (at least 18 months). The discovery of RMP embodied a revolutionary change in the treatment of TB [2]. The introduction of this drug resulted in earlier sputum conversion [19]. However, the main progress was that treatment length was reduced to 6–9 months [20]. This new successful strategy was termed ‘short-course chemotherapy’ [21]. This regimen consisted of INH and RMP for 6 months with a 2-month intensive phase with pyrazinamide (Z). It demonstrated efficacy of over 95% in patients with drug-susceptible TB. The adverse reaction rate was lower than 2–3% [22]. This is Category I treatment; the regimen for new cases from the WHO [23].

The bacteriological reasoning, previously explained, provides two fundamental approaches: the use of several drugs avoids the development of resistant strains, while long treatment periods kill dormant populations, reducing the risk of relapse [2]. It was demonstrated that the combination of three effective drugs was sufficient to avoid resistances; however, this was described in ideal conditions where all M. tuberculosis strains were totally susceptible. The circumstances have had notable changes over these three to four decades; a considerable proportion of patients holding M. tuberculosis drug-resistant strains have not previously been treated [6]. There is common agreement that, unless there are ideal conditions and evidence that there is no resistance within the community, TB treatment should include at least four drugs [4]. This rule should be applied to all TB cases. This is the principal reason that justifies the addition of EMB in the intensive phase of Category I.

If there is resistance to INH (the most active drug for killing metabolic forms of bacilli) and RMP (the most powerful sterilizing drug), longer and less effective treatments are required. In this case, it is necessary to use the remaining most potent drugs to kill active and dormant bacilli. These are fluoroquinolones (FQs) and second-line injectable agents (second-line aminoglycosides and polypeptides). Again, if resistance emerges to any FQ and any second-line injectable over an already MDR-TB case, the treatment possibilities become seriously limited. These strains are defined as XDR-TB [24].
MDR-TB as a public health problem: the impact of HIV

With the advent of RMP, in many wealthy countries that had strong primary healthcare services, TB was tackled and research was stopped. At the same time, as it has been outlined previously, patient resistance to RMP and INH began to appear. These were isolated problems in settings where high numbers of patients were treated. In an attempt to treat these limited cases, drugs developed in the 1950s and 1960s were used. Drug resistance management remained without substantial changes over several decades.

Gradually, the inefficient individual treatment of those few cases created a vast prevalent group in some countries. Non-implementation of DOTS, irregular or poor-quality treatments and other circumstances converted this individual problem into a public health concern (Box 1). Outbreaks of MDR-TB began to be reported. Finally, in the 1980s, the appearance of HIV changed the TB landscape. It is known that macrophages and CD4 lymphocytes are the main cell targets for HIV, which are also the principal barriers put up by the immune system to stop TB disease progression. Therefore, HIV acts synergistically to destroy the principal protection against TB. In fact, people living with HIV/AIDS are more likely to get infected and are 100–140-times more likely to develop the disease and also to die as a result of it [2,25].

Well-documented outbreaks of deadly MDR-TB among HIV/AIDS patients occurred in many settings and increased concerns regarding the disease and the attention paid to it on a global scale [26–28]. TB-control programs were strengthened in developed countries. At the same time, there was a steady introduction of antiretroviral therapy (ART) and great efforts were made in HIV-prevention, focusing on risk groups. The situation was partially controlled, while in developing countries, little or no information was available.

Simultaneously in the 1980s, FQs were discovered and proved useful not only for susceptible TB, but also for resistant strains [29,30]. Invariably, FQ discovery has thus far been the main achievement in MDR-TB treatment [31,32], but the irrational use of these drugs for other infections and among TB patients has aggravated the problem, thus promoting the emergence of XDR-TB.

Due to concerns surrounding the increase in DR-TB, WHO and The Union started projects to survey the global drug-resistant TB burden. To date, there are four world DR-TB reports that clearly indicate the extent to which the problem is growing annually [6]. Regardless, the issue only reached the international agenda in 2006, when the Centers for Disease Control and Prevention presented the rise of XDR-TB [33]. Shortly after that, a well-documented deadly XDR-TB outbreak in South Africa occurred [9]. The death rate was as high as 98% among HIV-infected patients in less than 4 weeks from diagnosis. Moreover, the genetic studies revealed that the strains were the same, hence the transmission was person-to-person, most likely within a health facility. These circumstances promoted the issue to the top of the international agenda, as the HIV collectives and the pharmacy industry considered that ART achievements could be hampered by untreatable TB, with a return to sanatoria times. In October 2006, a meeting was held where actions where taken and XDR-TB was redefined [24].

Box 1. Common factors associated with selection of TB resistance in the community.

- Poorly implemented directly observed treatment short-course strategy
- Poor adherence and supervision of treatment
- Nonstandardized treatments
- History of frequent shortages of drug supplies in the country
- Poor quality of anti-TB drugs
- TB treatment mainly performed in the private sector
- Inefficient hospital infection control
- High prevalence of highly virulent strains of *Mycobacterium tuberculosis*
- HIV infection in some settings

Adapted from [37].

Currently, the estimated number of MDR-TB cases worldwide is the highest ever reported (489,139 cases) [5,6]. The global proportion of resistance among all cases has grown to 4.8% (95% CI: 4.6–6.0). China and India alone carry approximately 50% of the global burden, and the Russian Federation a further 7%.

To date, XDR-TB has been reported in 49 countries since 2002 [6,34]. Data on DR-TB are unknown for more than 100 countries due to the unavailability of quality laboratories. Estimates have a high level of uncertainty and are probably underestimated in unsurveyed countries [5]. Most MDR-/XDR-TB patients remain undiagnosed and untreated [6,35]. Airborne spread of XDR-TB in a world with greater human movement and more relaxed border control is increasing a global concern.

Risk factors for drug-resistant TB

Identifying the individual factors leading to MDR-/XDR-TB is crucial to address suitable case-finding strategies. To date, the better documented worldwide risk factor for DR-TB is having been previously treated for TB [5,6,35–37]. However, being a close contact of a DR-TB patient is another major risk factor [38,39]. In some settings, the private sector could be playing a relevant role in drug-resistance acquisition, as it tends to manage TB without DOTS and works outside of international and national TB standards of care [40,41].

HIV was not considered to be itself a risk factor for infection with MDR-TB at an individual and ecological aggregated level [35,56]. Conversely, more recent but limited data seem to suggest that HIV could be a risk factor [6]. Nevertheless, the association between HIV and MDR-TB could be explained by environmental factors, such as transmission in congregate settings [42]. Countries with a high burden of HIV are susceptible to DR-TB. There is more information concerning individual risk factors in Box 2.

However, there are many other reasons for the global increase, such as poverty, substandard national TB programs (NTPs), stock ruptures, lack of access to primary public health services, inadequate treatment regimens, irrational drug use and INH monoresistance [35,37,43]. Many of these reasons are also listed in Box 1.
Box 2. Individual risk factors for TB-resistance.

- Failures of category II and chronic patients
- Exposure to a known MDR-TB case
- Failure of category I treatment
- Failure of anti-TB treatment in the private sector
- Patients who remain smear-positive at the second or third month of treatment
- TB relapses and retreatments after default
- Exposure in institutions that have MDR-TB outbreaks or a high MDR-TB prevalence (e.g., prisons)
- Residence in areas with high MDR-TB prevalence
- History of using anti-TB drugs of poor or unknown quality
- Treatment in programs that operate poorly (especially out-of-stock drugs)
- Comorbid conditions associated with malabsorption
- HIV in some settings

*Category II: WHO standard treatment for previously treated patients.
†Category I: WHO standard treatment for new patients.
‡MDR: Multidrug-resistant.

Adapted from [35,36,47].

Approach to the diagnosis of patients with drug-resistant TB

One of the main challenges in DR-TB is the diagnosis, as clinical symptoms and basic TB diagnosis tools (sputum smear and chest x-ray) of susceptible cases do not differ from resistant cases. Currently, the principal method of discerning resistances is through bacterial culture and drug-sensitivity testing (DST). DST can be performed in Lowenstein solid culture or in more rapid liquid culture mediums. Nevertheless, both techniques are lengthy (ranging from 10 days to 2 months) for clinical purposes. Culture and DST are complicated and expensive techniques. Moreover, DST must be performed only at quality-assured laboratories with good, safe facilities and equipment. Additionally, in vitro DST often shows poor reproducibility and lack of correlation with clinical response. This is especially true for second-line anti-TB drugs (SLDs) [44]. DST validity varies widely depending on the specific drug tested and the resistance prevalence [4,45,46]. In fact, the latest WHO MDR-TB guidelines do not recommend the use of DST for EMB, Z and the drugs in group 4 and 5 to base individual regimen design (Box 3) [47]. A complete history of anti-TB drugs used by the patient and prescribed in the country is a fundamental tool to complement and confront the information provided by the DST. These data could be relevant in clinical practice, as the use of an anti-TB drug for more than 1 month is thought to be one of the main resistance predictors. Fortunately, the most reliable DST results are for INH and RMP [4,45,46] and many efforts are put towards SLDs DST standardization.

However, these drawbacks, in addition to information and logistical problems, create critical clinical delays in resource-constrained settings [2,48].

A wide range of novel diagnostic techniques to obtain faster and valid diagnoses have been introduced. Probably the most promising for high-burden countries (HBCs) is genotypic rapid DST, which detects mutations linked to phenotypic drug resistance. These tests are line-probe assays that provide quick (1–3 days) and cheap results to identify resistance with a high level of reliability. The better-documented mutations are in the rpoB gene, which is responsible for 95% of RMP resistances [49]. Moreover, a positive rapid test for RMP resistance is a strong indicator of MDR-TB [50,51].

The main advantages of quick RMP resistance detection would be the early identification of patients at risk of DR-TB, such as those with treatment failures and previously treated patients. Thus, MDR patients could receive early treatment, avoiding amplification and achieving a prompt interruption of MDR-TB transmission [47]. Recent studies on the commercially available Genotype® MTBDR (GT-MTBDR) and its new, more sensitive version (GT-MTBDRplus) open the door for the use of these techniques as MDR-TB screening tools in developing countries [52,53].

Sampled directly from the smear, the genotypic tests were trialled in a busy routine diagnostic laboratory in South Africa against conventional liquid culture and DST on solid medium [52]. It provided results in 1–2 days in 97% of cases. Sensitivity, specificity and positive and negative predictive values for MDR-TB detection were 98.8, 100, 100 and 99.7%, respectively, compared with conventional procedures. These molecular techniques have demonstrated the potential to be used as screening tools for MDR TB, with substantial reduction in diagnostic delays and substantial cost savings. Genotypic approaches could also be a way to diagnose rapid development of resistance to SLDs. Shortly, a rapid test for FQ resistance mutations will be available. Nonetheless, other SLDs rapid tests are still under development.

Once more, the problem in HBCs is not only the cost of the technology itself but the infrastructure, the maintenance and human resources need. However, even with the useful rapid diagnosis, it would not be enough in low- and middle-income countries (LMICs), as in many occasions just the time taken in the delivery of results is doubled due to inefficient information mechanisms in NTPs [48].

Management of patients with drug-resistant TB: lessons learned from past evidence

As previously stated, most of the evidence on which current recommendations are based date from the 1960s when RMP and FQ were not yet discovered [4,54]. Moreover, the diversity of resistance patterns within countries makes standardization even more difficult. On top of this, management of MDR/XDR-TB cases is lengthy and quite complex. Thus, it should be only carried out by experienced staff [2,4]. Nevertheless, in LMICs with very-high TB burdens, the number of possible MDR cases is so high that it cannot be managed by specialists alone [45]. Therefore, standardization is vital but, given the current tools and evidence, it is not easy to create strong and universal recommendations. In order to approach MDR-TB management, it is essential to take into account the subsequent six controversial issues [4]. There is a brief summary of these in Table 1.

The first challenge is how to approach diagnosis of MDR-TB given that the DST has limited reliability. Comparing the information provided by DST plus the drug history enhances the likelihood...
of choosing the correct drugs. Detailed patient history and RMP- and \( \text{INH} \)-resistance confirmation should always be performed prior to MDR-TB treatment [4,45]. Whenever possible, DST to second-line injectables and FQ is strongly recommended.

Second, it is important to determine how many drugs should be used. The answer differs greatly according to patient history and the effectiveness of remaining susceptible drugs. There are substantial differences in resistance pattern among MDR/XDR-TB cases. According to evidence from countries with a low pattern of resistance to SLDs, three effective drugs were enough for an efficacious treatment, while in countries with great resistance to SLDs, a low number of drugs used was associated with worse outcomes [55]. As a common recommendation in NTPs, SLDs treatments should include ‘at least four drugs’ to which the \( \text{M. tuberculosis} \) isolate is known to be susceptible or, in the absence of DST, drugs that the patient has never used before for more than 1 month [4,11]. Occasionally, when several drugs could have their efficacy compromised or have very weak action, it may be justified to use more than four drugs to strengthen the regimen [4].

The third question to assess is which drugs to select on a rational basis. Drugs differ in efficacy and are classified into five groups (Box 3) [4,47]. ‘At least four drugs’ should be used and selected starting from group 1 (oral first-line drugs [FLDs]) and moving on to the next group when no adequate drug remains in the previous group. Groups 2 (injectables) and 3 (FQs) are the basis of SLD treatments. Only one drug from each group (2 and 3) should be used, since all drugs from the same group have the same genetic target. In addition, there is risk of cross-resistance and additive toxicities while no additional efficacy is gained.

To complete the ‘at least four drugs’ rule, group 4 medicines should be used, which have lower efficacy and are relatively toxic. If there is no other option, drugs from group 5 should be used, despite having very low or no documented efficacy. \( Z \) is frequently used on SLD treatments as it is usually used in combination with other drugs, and hence there is a chance of susceptibility. However, \( Z \) should not be counted as one of the ‘at least four’ drugs given that the patient has used it before for more than 1 month and it is not possible to assume total susceptibility.

At this point, it is important take into account the possibility of cross-resistances. Be aware that all rifamycins have very high levels of cross-resistance. At the same time, cross-resistance between old-generation FQs seems to be almost complete (e.g., ciprofloxacin and ofloxacin). However, limited evidence suggests that third-generation FQs (particularly moxifloxacin) do not have complete cross-resistance with the older generations. Regarding other drugs, ethionamide and protonamide have complete cross-resistance while ethionamide and \( \text{INH} \) present crossresistance when the \( \text{inhA} \) mutation is present [47]. Concerning injectable agents, cross-resistance is complex and evidence for it very limited. The most logical path on injectable use to avoid cross-resistance seems to be to start initially with capreomycin, then kanamycin and, finally, amikacin [56].

In relation to the length of the injectables (intensive phase) [4,47], the evidence is especially controversial and no RCTs are available. The most common recommendation is to continue using injectables at least 4 months after sputum or culture conversion, defined as two consecutive negative smears and cultures taken 30 days apart. After that, the injectable can be safely withdrawn when at least three effective drugs remain on the regimen. Nevertheless, if less than three effective drugs are available or belong to group 5, lengthy treatments with injectables should be considered. Intermittent therapy (three times a week) can be considered in the case of high risk of toxicity [47].

The fifth controversial issue is the role of the surgery. Despite the absence of RCTs, surgery is only indicated in very exceptional circumstances [4,47]. The most accepted recommendations for surgery are that it should be used only when there are not four drugs available, lesions are isolated and localized and when there is sufficient respiratory reserve [4,47]. Even in this situation, it must be remembered that surgery has high morbidity–mortality and the lesions are not sterilized [4]. An interesting and recent study performed in Peru concludes that the key factor for successful surgery in MDR-TB programs in LMICs is the appropriate selection of candidates [57]. These results are remarkable, as the previous literature addressing this issue were based in wealthy countries with exceptional levels of support and expertise – circumstances that could reduce the complication rates [32].

The last issue is the manner in which to approach the ideal regimen in MDR-TB – in other words, whether to use standardized or individualized treatments. Both are adequate, but it depends

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**Box 3. Rational classification of anti-TB drugs.**

<table>
<thead>
<tr>
<th>Group 1: first-line oral agents</th>
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<tbody>
<tr>
<td>• Isoniazid (H)</td>
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<tr>
<td>• Rifampicin (R)</td>
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<tr>
<td>• Ethambutol (E)</td>
</tr>
<tr>
<td>• Pyrazinamide (Z)</td>
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<tr>
<th>Group 2: injectable agents</th>
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<tbody>
<tr>
<td>• Kanamycin (Km)</td>
</tr>
<tr>
<td>• Amikacin (Am)</td>
</tr>
<tr>
<td>• Capreomycin (Cm)</td>
</tr>
<tr>
<td>• Streptomycin (S)</td>
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<tr>
<th>Group 3: fluoroquinolones</th>
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<tbody>
<tr>
<td>• Ofloxacin (Ofx)</td>
</tr>
<tr>
<td>• Moxifloxacin (Mfx)</td>
</tr>
<tr>
<td>• Levofloxacin (Lfx)</td>
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<tr>
<th>Group 4: oral bacteriostatic second-line agents</th>
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<tbody>
<tr>
<td>• Ethionamide (Eto)/protonamide (Pto)</td>
</tr>
<tr>
<td>• Cycloserine (Cs)/terizidone (Trd)</td>
</tr>
<tr>
<td>• p-aminoosalicylic acid (PAS)</td>
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<table>
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<tr>
<th>Group 5: agents with unclear efficacy</th>
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<tbody>
<tr>
<td>• Clofazimine (Cfz)</td>
</tr>
<tr>
<td>• Linezolid (Lzd)</td>
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<tr>
<td>• Aminocillin/clavulanate (Amx/Clv)</td>
</tr>
<tr>
<td>• Thioacetazone (Thz)</td>
</tr>
<tr>
<td>• Imipenem/cilastatin (Ipm/Cln)</td>
</tr>
<tr>
<td>• High-dose isoniazid (high-dose H)</td>
</tr>
<tr>
<td>• Clarithromycin (Clr)</td>
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</table>

Adapted from [4,47].

MDR-/XDR-TB management

Perspective
on the patient pattern of resistance, the economic NTP conditions and the clinical conditions of the patient. For instance, in an HIV-infected or a critically ill patient, an individualized treatment can be followed based on the drug history while waiting for DST results. While for MDR-TB cases receiving only FLDs in the past, it is perfectly appropriate to use standardized SLDs regimens, in MDR-TB cases receiving FLDs and many SLDs in the past, an individualized SLD regimen approach is preferred. In the case of initial MDR-TB coming from an MDR-TB contact, the treatment should be based on the same pattern of resistance as in the index case, if known [4].

Concerning other issues, treatment fundamentals for children do not differ from those for adults. Despite little evidence, all of the previous statements can be applied to children. At the same time, the role of corticosteroid in MDR-TB remains equal to its role in susceptible TB: coadjuvant in cases of severe respiratory insufficiency, CNS and pericardial involvement [47]. On the other hand, nutritional support and comprehensive and psychosocial approaches are strongly linked to good outcomes on these lengthy treatments [47,58]. Nevertheless, comprehensive and psychosocial approaches are mostly only possible in highly organized healthcare systems. Additionally, infection control (beyond the scope of this review) is likely to be one of the most cost-effective measures, especially in healthcare settings with a high HIV burden [47].

Finally, one of the most important and unresolved questions is how to proceed with MDR-TB infected cases. Currently, WHO guidelines recommend close supervision, but little is known about possible chemoprophylaxis [47]. This could again be a key issue, especially in high HIV-burden countries.

Overall, addressing these six questions enables the development of a rational approach to MDR-TB programs and treatments. However, different countries would require different strategies, depending on the type and levels of resistance and the resources available.

Prognosis
Invariably, MDR-TB and XDR-TB have worse outcomes than pan-susceptible TB for several aforementioned reasons. Gradually, more factors are described in the literature that are linked to good and bad outcomes (Box 4) [59]. However, MDR-TB and XDR-TB definitions were established due to different treatment needs and also due to different prognosis. Usually, XDR-TB patients have a potential treatment success rate lower than 50% [31,32,55,60] and clearly stand apart from MDR-TB patients. In addition, two recent studies have shown that the current XDR-TB definition is predictive of a poorer clinical outcome compared with MDR-TB [60,61]. Nevertheless, the current XDR-TB definition leaves open the possibility of treatment with FQs and injectables in the cases of incomplete cross-resistance throughout drug groups 2 and 3. Also, XDR-TB patients, by definition, could use FLDs other than RMP and INH, which lead to better outcomes [60]. Therefore, both groups under certain circumstances could obtain similar cure rates, as is currently being documented in Peru [58]. Probably, a more suitable definition for XDR-TB is needed [54]. Concerning relapses after SLDs treatment, very little is known, and studies on this question are also needed.

Relevant & recent evidence on DR-TB management
Concerning RCTs, there are several ongoing trials that are testing different treatment schedules in distinct settings. However, as yet there are no results available. A RCT on the effects of high doses of INH as an adjuvant therapy in MDR treatment has been published recently [62]. The study compared high INH (16–20 mg/kg/day) versus regular (5 mg/kg/day) INH dose versus no INH (placebo) in MDR-TB patients, in addition to SLDs. The results stressed the positive benefit, especially in significantly increasing (p < 0.001) the speed of sputum conversion, maintaining the equal overall toxicity in all groups. In fact, this is not the only publication addressing these lengthy treatments [47,58]. Nevertheless, comprehensive and psychosocial approaches are mostly only possible in highly organized healthcare systems. Additionally, infection control (beyond the scope of this review) is likely to be one of the most cost-effective measures, especially in healthcare settings with a high HIV burden [47].

Table 1. Multidrug-resistant-TB management: fundamental aspects.

<table>
<thead>
<tr>
<th>Step</th>
<th>Considerations</th>
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<tbody>
<tr>
<td>1. Diagnose</td>
<td>Compile and compare information History of drugs: 1 month intake of a failed drug regimen could be a strong predictor of resistance DST: most reliable for R and H; also reliable for Km and FQ; less reliable for E and Z; very low reliability for group 4 drugs</td>
</tr>
<tr>
<td>2. Number of drugs</td>
<td>At least four effective drugs</td>
</tr>
</tbody>
</table>
| 3. Drug selection     | Use FLDs if they are still effective  
                          One injectable  
                          One FQ  
                          Use group 5 drugs until complete four effective drugs  
                          If necessary, use group 5 drugs to strengthen the regimen, or when no four effective drugs are reached with the previous groups |
| 4. Length of the injectable | At least 4 months after smear or culture conversion; longer if there are no three effective drugs during continuation phase or are from group 5 |
| 5. Surgery            | Consider only if:  
                          Few effective drugs are available  
                          Localized lesions  
                          Sufficient respiratory reserve |
| 6. Ideal regimen      | Standardized: if there is no use of SLDs in the past  
                          Individualized: use of SLDs in the past or contact of a MDR-TB patient who had use of them (treat with the effective regimen of the index case) |

DST: Drug-sensitivity test; E: Ethambutol; FLD: First-line drug; FQ: Fluoroquinolone; H: Isoniacid; Km: Kanamycin; MDR: Multidrug-resistant; R: Rifampicin; SLD: Second-line drug, Z: Pyrazinamide.

Adapted from [4,47].

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\text{Perspective} \\
\text{Monedero & Caminero}
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Regarding other sources of evidence, there are many personal experiences and case studies available about DR-TB in the hospitals of developed countries. However, little is known about MDR-TB in NTPs in developing countries, although some illustrating experiences have brought important knowledge on DR-TB management. For example, in 2002, the publication of the Peruvian experience, showed that for the first time, standardized MDR-TB treatment was widely provided by a NTP in a LMIC [64]. It was shown how MDR-TB treatment, under a suitable NTP, was possible, and even highly cost-effective, with acceptable success rates in resource-constrained settings. In 2004, the results of a cohort of 58 MDR-TB cases using standardized treatment in Bangladesh, which achieved outstanding cure rates (69%), was published [65]. This study highlighted the success of novel approaches to treating MDR-TB, such as high doses of INH, clofazime use and the importance of early treatment of SLD side effects during long treatments.

In 2005, the MDR-TB experience of Latvia was presented. This country had an extraordinarily high MDR prevalence and patterns of resistance to many drugs [55]. Three-quarters of MDR-TB patients enrolled at NTP conditions obtained successful outcomes, even as a resource-constrained setting. Based on an individualized approach, many fundamental issues arise from this study. For example, it was shown how the survival rates were linked to the number of effective drugs used and the pattern of drug resistance. In addition, resistance to ofloxacin was linked to poor outcomes, providing a view of how important FQs could be for MDR-TB treatment.

More recently published, in 2008, are the treatment outcomes of 603 MDR-TB and 48 XDR-TB patients in Peru. They were treated in Lima between 1999 and 2002, being NTP-managed on an outpatient basis [58]. In contrast to the previous evidence, the striking result was statistically similar outcomes for MDR-TB and XDR-TB patients (66.3 vs 60.4%; p = 0.36). It has been shown how XDR-TB can be cured in HIV-negative LMIC populations. It is also important to remark upon the comprehensive patient approach adopted in Peru, which offers socio–economical and psychological support. Based on an individualized approach, many fundamental issues arise from this study. For example, it was shown how the survival rates were linked to the number of effective drugs used and the pattern of drug resistance. In addition, resistance to ofloxacin was linked to poor outcomes, providing a view of how important FQs could be for MDR-TB treatment.

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**Future: mathematical models**

In considering this global increase, one important question arises: do resistant strains have the same infectious capacity as susceptible strains?

Given that the major mechanism underlying DR-TB is mutation, the infectious capacity of the microorganism could be reduced. For example, mutations on the *rpoB* gene (the main

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**Box 4. Predictors of good and poor outcomes in the treatment of multidrug-resistant TB.**

### Predictors of poor outcome
- In vitro resistance to FLD and SLD
- Resistance to ofloxacin
- Cavitary and bilateral disease
- Treatment with less than two active drugs or the use of five or fewer drugs for 3 months or more
- XDR-TB and MDR-TB versus not-MDR-TB
- Low BMI
- Capreomycin resistance of XDR-TB
- Kanamycin resistance
- Higher number of drugs received previously
- Having previously received treatment for MDR-TB
- Male gender
- Age older than 45 years
- Low hematocrit level
- Poor clinical condition
- HIV coinfection
- MDR-TB status knowledge at the time of diagnosis
- Extrapulmonary localization
- Underlying comorbidity
- Patients whose initial regimen was changed due to adverse drug reactions
- Receiving category I versus category II treatment
- Alcohol consumption during treatment
- Poor adherence
- Positive sputum cultures after 2 and 3 months

### Predictors of good outcome
- Fluoroquinolone therapy
- Absence of previous treatment with ofloxacin
- Surgical resection
- Inclusion of pyrazinamide and ethambutol in the regimen (when susceptibility was confirmed)
- MDR-TB cases susceptible to at least one FLD
- To receive appropriate therapy for more than 2 consecutive weeks
- Negative sputum cultures after 2 and 3 months of therapy
- Patient admission
- Resistance pattern
- Younger age
- Hospitalized in a specialized centre
- Older patients
- New MDR-TB cases
- Treatment for 12 months
- Higher level of albumin
- Normal BMI
- Use of more than four drugs

**Notes:**
- FLD: First-line drug; MDR: Multidrug-resistant; SLD: Second-line drug; XDR: Extensively drug-resistant.
- Adapted from [59].
mechanism conferring RMP resistance) have been shown to decrease growth speed and lower virulence in vitro [67]. The term fitness is more appropriate as this takes into account not only virulence, but also transmissibility. Nevertheless, experiences have shown that prolonged patient treatment can result in MDR-TB strains with no changes in fitness. Clinical experiences have shown that DR-TB strains with no changes in fitness are also the most common [68].

Independent of virulence, according to estimations, MDR-TB patients have three-times higher transmission than susceptible-TB patients, since those who have been unsuccessfully treated live longer with the disease and consequently infect more people [69]. Modeling epidemics of MDR M. tuberculosis of heterogeneous fitness have shown that, even when the average relative fitness of a MDR-TB strain is low, and a well-functioning control program is in place, a small subpopulation of a relatively fit MDR-TB strains may eventually outcompete both the drug-susceptible strain and the less-fit MDR strains [70]. Furthermore, current trends and studies predict the possible shift from susceptible to untreatable strains [71]. Mathematical modeling suggests that current annual incident rates may climb even with intensive efforts to control the disease [72]. This is not an isolated problem in HBCs where most of the MDR-TB cases come from. Globalization and population mobility predict a worldwide increase in MDR-TB [73,69].

Other mathematical models predict exponential increases in XDR-TB internationally as a result of synergistic interaction of acquired resistance due to SLDs treatment and transmitted resistance [71,74,78]. Without tight control of MDR-TB epidemics, XDR-TB would quickly become uncontrollable [71]. One of the models was created to compare DOTS with MDR-TB program component (former DOTS-Plus) [75]. The model found that in LMICs, suboptimal DOTS-Plus could quickly lead to developing XDR-TB with decreasing effectiveness of the whole TB program. Additionally, several clinical experiences and modeling programs identified that poor treatments can be worse than no treatment. A narrow focus on MDR-TB therapy could paradoxically make a bad situation worse [17,72].

This problem could be partly solved by a substantial increase in monitoring, evaluation and capacity building. However, this does contribute to the other main risk: the diversion of resources away from DOTS. If MDR-TB program implementation comes with just a 5% decrease in regular DOTS effectiveness, the cumulative number of deaths would be substantially higher than if DOTS was implemented alone [75]. The consequences of the diversion of funds and human resources could be the increase in deaths in susceptible TB patients and the creation of more MDR-TB as a consequence of DOTS failure [71,75–77]. In fact the success of advocacy for MDR-TB treatments programs has forced some governments to initiate MDR-TB treatment prematurely, before robust DOTS strategies are already built [72]. On the other hand, in hot zones (>10% of primary drug resistance), optimal MDR-TB programs would have a great impact on lowering total TB mortality [71,75]. According to these models, best DOTS practice is highly likely to control MDR-TB and can even prevent its emergence. In agreement with the mathematical models, we consider that the key in fighting MDR-TB is to not create it. However, once DR-TB has emerged, even the best DOTS practice cannot contain DR-TB outbreaks. In such cases, SLDs are required to prevent MDR-TB outbreaks [77].

**Expert commentary**

Multidrug-resistant/extensively drug-resistant TB is clearly an emerging problem. Currently, there are more controversies than certainties, but clearly more solid evidence validating various recommendations will come to light in the near future. Moreover, increased political interest, funding, and research and development are starting to flow towards TB for the first time in several decades.

Interventions to increase early identification of resistant TB could play an important role. For example, rapid detection of the rpoB mutation could simplify and hasten the classification of patients. If rpoB detection could be available at cheap prices without high-tech requirements, it could substantially change the procedures in LMICs. In particular, laboratory requirements, capacity and delays are one of the major bottlenecks in MDR-TB programs in LMICs.

The results of ongoing trials on current drug schemes could also be very important for the future management of TB. The role of FQs is increasingly studied. Ciprofloxacin is not recommended anymore to MDR-TB as other FQs have shown much better profiles [47]. At the same time, levofloxacin 1000 mg (double regular dosage) is showing similar efficacy to moxifloxacin with a reduction in total costs [78]. However, the actual role of the new FQs in the initial phase of treatment remains unclear [30,78]. It is necessary to address whether new-generation FQs, such as gatifloxacin and moxifloxacin, could have similar sterilizing activity to RMP. In that case, MDR-/XDR-TB treatment length could be substantially reduced without an increased relapse risk. In addition, it is vital to confirm if the introduction of a new FQ could reduce the duration of susceptible TB treatment to 4 months. An issue arising is the extent of the risk of cross-resistances and amplification against the increase in adherence due to the length reduction.

Another interesting issue remaining is the unclear role of clofazimine [79], a drug included in group 5 but that could probably be placed in group 4. There is little evidence on this matter and clofazimine, as well as high doses of INH [62], could play a relevant role in the near future, as was shown in Bangladesh [69]. In addition, linezolid, a group 5 drug, could be a promising tool, especially in XDR-TB treatment [80,81]. However, to date little evidence is available, especially regarding its effectiveness when using lower, and therefore safer, dosages [82]. However, the price of this drug and its grave side effects make it an unsuitable candidate for most HBCs.

There are several new and promising drugs in the pipeline [83]. New rifamycins, such as rifalazil (KRM-1648), have shown efficacy and long-acting oral activity against M. tuberculosis. Rifalazil is currently under Phase II clinical trials. Another good example is the novel compound PA-824, which has demonstrated potent activity against active and dormant forms. At this moment, PA-824 is going through Phase II clinical trials. An additional...
component currently in Phase II clinical trials is TMC207, which seems to have a very specific antimycobacterial mechanism in combination with a long life, which could allow weekly treatments and possibilities to reduce the length of treatment. However, these and other new compounds will not be completely tested within the next 5–10 years. Therefore, it is very unlikely that new drugs will be ready for clinical use in LMICs in the next 10–15 years. Vaccination could certainly be the best tool to tackle TB and many efforts are following this approach. Once again, this will take at least 10–20 years to be introduced in LMICs. There will be no ‘magic bullet’ to control MDR/XDR-TB and, hence, it is more realistic not to simply wait for new TB drugs or vaccines. It is important to simplify DR-TB management and gradually incorporate standardized treatments into the procedures applied in the NTPs [4]. Low-cost and low-risk policies to optimize current tools could be essential to prevent DR-TB scale-up and improve its management. Some of these affordable interventions to reduce the risk and dimension of the DR-TB problem could be:

• Strength DOTS. More than ever, high-quality DOTS is necessary to cure susceptible patients and prevent MDR [37];

• Wide use of fixed-dose combinations (FDCs). Recently, in the 39th World TB Conference, the provisional results from The Union’s ‘Study C’ were publicly shown [85]. This RCT was performed with high-methodology standards covering a population approximating 1400 patients in 11 different settings. Based on a noninferiority analysis, it has been demonstrated that FDCs have similar effectiveness and side-effect profiles as loose drugs. FDCs have key logistic and practical advantages and the obvious capacity to avoid monotherapy [86]. Added to the currently reduced price, one can speculate that if FDC uptake increases, especially in the private sector in LMICs, cure rates could also increase and, at the same time, a substantial proportion of drug-resistant TB cases could be prevented;

• Engage all healthcare providers in TB, especially pneumologists and those in the private sector. The influence of the private sector on DR-TB remains unclear but, without any doubt, it plays a crucial role as NTPs are not enough in the fight against TB. Formal and informal private sectors hold a substantial number of patients worldwide and, thus, even in the absence of DOTS, the daily use of FDCs under suitable protocols with proper referral systems added to strong capacity building with monitoring and evaluation activities could bring remarkable benefits in cure rates and DR-TB reduction;

• Perform rapid DST (at least to RMP) to all failures, defaults, relapses, TB patients contacts from a MDR case and to all smear-positive cases in areas of high MDR prevalence. Rapid test screening could improve early case detection, avoiding unnecessary category II treatments, reduce further resistance amplification and maximize prevention of MDR-TB infection in the community. If the resources are available, another possibility to identify MDR-TB cases early could be performing rapid DST to all smear-positive cases at the end of the second month of the Category I regimen;

• Extend intensive-phase treatment by 1 month in sputum smear-positive cases at the end of the second month of treatment. An additional month with four drugs could reduce the bacterial load and, in the eventual case of monoresistance (especially to INH), the likelihood of gaining resistance to RMP in the continuation phase would very probably be reduced. In the case of extensive lesions or fibrotic lesions with bad drug pharmacokinetics, it would be beneficial, while, in the case of dead or nonviable bacilli, no substantial change would occur;

• Moreover, in LMICs where initial INH monoresistance rates are high, it could be reasonable to add EMB during the whole continuation phase. In theory, adding EMB, which is a cheap and well-tolerated drug, could reduce the risk of MDR development over initial INH resistance, protecting the RMP during the continuation phase. We believe that the potential benefits from adverted MDR-TB could outweigh the increase in cost, side effects and toxicity in countries with high initial INH or INH plus SM resistance rates.

Five-year view
TB is again on the international agenda and now more than ever joint efforts and funding are starting to be directed towards research and development against TB. However, in the race against DR-TB, we have started with decades of delay and been helped only by outdated tools. A quick sprint is currently necessary to overcome the disease before it is too late. Unfortunately, DR-TB treatment lasts an average of 2 years, so the impact evaluation of interventions and treatment outcomes, especially relapses, could take many years. In addition, clinical trials and the development and testing of new drugs or vaccines could take decades. It is unlikely that significant changes in the TB landscape will be witnessed in the next 5 years. During the next 5 years, more experience on current diagnoses and treatment will be gathered but, nevertheless, it is expected that some RCTs will be completed that will improve the evidence on which current recommendations are based.

Furthermore, the future of the TB epidemic will be linked to HIV evolution, poverty and migration circumstances. All of these are closely related to geopolitical and economical circumstances. Nevertheless, even with obsolete tools in LMICs, there is still a vast amount to be done. Optimizing current tools and strengthening primary healthcare systems and DOTS programs could improve or at least reduce the rise of the MDR/XDR-TB epidemic. Despite warnings of mathematical models, there is a positive future if there is continuous political will and the provision of funding towards this disease.

Financial & competing interests disclosure
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Key issues

- Drug-resistant TB is a manmade problem related to inadequate TB treatment or management. Efforts should be made to prevent multidrug-resistant (MDR)-TB, which usually relies on good directly observed treatment short course (DOTS) practice, early case-detection and high cure rates in national TB programs (NTPs).
- Management of MDR-TB patients is long and quite complex. It should be carried out only by experienced staff. Even if resources are unlimited, malpractice in NTPs can create more cases of MDR-TB and faster than they can be treated.
- MDR-TB may not necessarily be less virulent. MDR-TB and XDR-TB will be universal if we do not act appropriately now.
- Optimizations of current tools (DOTS expansion, fixed-dose combinations use, public-private mix, adapted treatments for high isoniazid resistance prevalence settings and rapid drug-sensitivity testing) appear to be, in the near future, the best option to prevent and manage resistant cases. There is an urgent need for new drugs and quick and reliable methods of diagnosis. Nevertheless, new drugs and vaccines could take decades to be developed and tested, and even more time to be implemented in developing countries.
- Summary of MDR-TB good practice:
  - Perform a comprehensive patient drug history and confirm by DST resistance to rifampicin and isoniazid (and if possible to ofloxacin and kanamycin in MDR-TB in high-burden countries)
  - Use ‘at least four effective drugs’. If possible, use first-line drugs and include one fluoroquinolone and one injectable (be aware of cross-resistance between different drugs of the same group)
  - Minimum length of injectable: from 4 to 6 months after sputum/culture conversion. Whole treatment should last 18 months after culture conversion
  - Close supervision and treatment of side effects
  - Never add a single drug to a failing regimen
  - Comprehensive and psychosocial approach
- Standardized versus individualized treatment. Both can be applied; however, the key factor is the appropriate patient selection. Patients never having used second-line drugs are suitable candidates for standardized regimens.
- Different countries, depending on their resources and the characteristics of their epidemic, require different case findings and treatment strategies.
- If well-performed and -managed, treatment of drug resistance is possible with more than acceptable success rates even in resource-constrained settings. However, a narrow-view focus on MDR-TB treatment could make a bad situation even worse. More than ever, high-quality DOTS is necessary.

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest


• Systematic review on the current knowledge of fluoroquinolones (FQs).

Important to understand the possibilities of FQs in MDR-TB and the reason for using new-generation FQs.


• Addresses the most common situations and mistakes leading to MDR/extensively drug-resistant (XDR)-TB at the clinical level. Establishes possible risk factors and basic interventions to limit the progress to MDR/XDR at the programmatic level.


• Updated guidelines on MDR/XDR-TB. A consensus document covering the most important aspects of the disease at all levels incorporating the most recent evidence. Fundamental guidelines to create and improve the effectiveness of MDR-TB response and programs.


First long-term study on MDR-TB surgery in developing countries. Indicates the most suitable circumstances for surgery in MDR-TB.


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Perspective

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