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Abstract: Multidrug-resistant tuberculosis (MDR-TB) is threatening control of TB in many parts of the world. As a result of limited treatment options, patients have a poor prognosis and low chances of cure. This situation can be exacerbated by HIV epidemics. In some cases, the risk exists of a real shift from susceptible to resistant strains. Despite its relevance, currently there are more contradictions and confusion surrounding MDR-TB than hard evidence. No randomized controlled trials have been performed and published evidence is limited. Rather than just the selection of expensive drugs, MDR-TB management requires well-structured programmes with a comprehensive approach, which involve the actions of a wide range of participants. Even with current investments in research and development, new drugs and vaccines will take many years to be applied in low and middle income countries. The most successful results will depend on the optimization of existing tools. The majority of the patients, even those with extensive patterns of bacilli resistance, have a possibility of cure if current clinical knowledge and effective logistics are applied. This paper is a critical review of current best practice regarding the diagnosis and treatment of MDR-TB.

Keywords: tuberculosis, multidrug resistance, extensive drug resistance, review, treatment

Background

Tuberculosis (TB) still affects more than 9 million people every year and kills nearly 2 million [WHO, 2009b]. At present, in 2010, we are still far beyond from controlling this old disease. The most concerning fact is that treating TB is not clinically complicated and a cure is possible for more than 95% of patients with first-line drugs (FLDs). FLDs were discovered in the 1950s and 1960s, whilst community control measures have been well known since the 1950s [Caminero Luna, 2004].

FLDs are currently the most potent and least toxic remedies for treating TB. The new case standard treatment is based on the use of four FLDs for 6 months [WHO, 2009c]. The duration can be limited to 6 months because of the powerful sterilizing capacity of rifampicin (RIF), which is the quickest effective TB treatment [Fox, 1981]. From a public health perspective, a 6-month treatment that needs full supervision requires strong primary health services. In 2010 however, basic primary health services are not universal, particularly in low- and middle-income countries (LMICs). Moreover, TB is

a disease strongly linked to poverty, whilst poverty is strongly linked to barriers in access to health services.

The result is that a curable disease with cheap (the average cost of full drug treatment is US\$20) and well-tolerated drugs is still rampaging through many societies. Furthermore, being a disease of the poor, little research and funding have been directed to TB since it was eliminated as a public health problem in developed countries [Monedero and Caminero Luna, 2009]. It is notable that the most effective drugs date from the 1960s and the most common diagnosis tool, the sputum smear, was discovered by Robert Koch himself.

After decades of FLD use, resistant bacilli populations are being selected mainly due to inappropriate treatments, such as monotherapy or masked monotherapy [WHO, 2008a]. The major problem arises when resistance to RIF and isoniazid (INH) occurs. This situation is defined as multidrug-resistant tuberculosis (MDR-TB). INH is the drug with the quickest and most bactericidal activity, thus it clinically

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cures and saves patients' lives. RIF is a strong bactericide. On top of it has the most effective sterilizing activity, killing the dormant and semi-dormant bacilli population [Caminero, 2005]. Accordingly, this results in a cure almost free of relapses. Once resistance to RIF occurs, 18–24-month treatments are required to kill dormant populations and achieve a cure without relapses.

MDR-TB used to be a limited problem localized in TB reference centres. However, after decades of use and misuse of FLDs, more than 500,000 MDR-TB cases emerge annually [WHO, 2008a]. This trend is rising in many settings. MDR-TB status remains unknown in more than 100 countries as a result of restricted laboratory capacity. Therefore, these estimates have a considerable degree of uncertainty and are most probably an underestimation [Zignol *et al.* 2006]. Mathematical models indicate that a change in strains from susceptible to resistant is possible [Blower and Chou, 2004]. In the absence of widely available new drugs, vaccines and diagnosis tools, MDR-TB is a major global public health concern.

As mentioned above, to cure an MDR patient takes 18–24 months with second-line drugs (SLDs), which are less efficacious, more toxic, less tolerated and considerably more expensive [WHO, 2008b]. Nevertheless, with improper treatment schedules or under certain circumstances, resistance could be amplified to SLDs. If fluoroquinolones (FQs) and second injectables, which are the most powerful SLDs, are lost, the prognosis of the patient is severely undermined. This pattern of bacilli resistance (MDR plus one of the FQs and at least one second-line injectable) is the current definition of extensive drug resistance TB (XDR-TB) [WHO, 2007]. Obviously patients with XDR-TB have fewer drugs available for their treatment and their prognosis tends to be poorer.

In September 2009, XDR-TB was reported in 57 countries [WHO, 2009a]. Given the current low capacity to diagnose and the reduced MDR-TB cure rates according to mathematical models, it is possible that the more MDR-TB is diagnosed, the more XDR-TB is created [Blower and Supervie, 2007]. There is a real risk of a TB difficult to cure and expensive. This should be considered a call to arms for better MDR management worldwide.

This article is a comprehensive and critical review of the most relevant and valid evidence in MDR-TB according to two independent researchers working internationally in this field. The aim of this paper is to provide a range of updated practices in MDR-TB management.

Approach to diagnosis

Unfortunately the current tools for MDR-TB confirmation are not easy to use, nor are they completely reliable, cheap or quick [Kim, 2005]. Hence diagnoses need to be optimized, especially in LMICs. To make a diagnosis more cost effective, the suspicion (the first step in diagnosis) should be based on a patient presenting the main risk factors for MDR-TB [Caminero, 2010]. To date the major risk factor is having had previous treatment for TB. The key risk factors in contracting MDR are failure to WHO Category II treatment and chronic cases (more than two cycles of RIF-containing treatment without getting cured) [WHO, 2008b]. The subsequent risk group corresponds to patients who are WHO Category I failures and TB patients probably infected by an MDR-TB index case. The third risk group in MDR-TB is represented by relapses, defaulters, patients who are smear positive at the end of the second month and have previously been treated in the private sector, those working in institutions with MDR outbreaks, patients coming from high primary MDR areas or patients treated under poor National Tuberculosis Control Programme (NTP) conditions [Caminero, 2010]. See Table 1 for more information regarding individual risk factors for TB resistance.

HIV is known to be linked to MDR-TB outbreaks but is not itself a risk factor [Suchindran *et al.* 2009]. Given that HIV is a disease that destroys the CD4 and macrophage (principal barriers to TB disease progression), the susceptibility of HIV patients towards TB disease increases by a hundred [Caminero Luna Ja. Paris, 2004; Selwyn *et al.* 1989]. A significant number of MDR-TB and even XDR-TB outbreaks with high mortality rates among HIV patients have been documented [Gandhi *et al.* 2006; Samper *et al.* 1997; CDC, 1994; Coronado *et al.* 1993].

Once the risk groups have been identified, it is important to note that sputum smear, chest X-ray or clinical facts do not differ from susceptible to resistant TB. MDR-TB is just a distinctive form of TB, which cannot be cured

Table 1. Individual risk factors for resistance.

- (1) Category II* and chronic patients
- (2) Tuberculosis (TB) cases with known close exposure to a multidrug-resistant tuberculosis (MDR-TB) case
- (3) Category I** failures
- (4) Failure of anti-TB treatment in the private sector
- (5) Patients who remain smear positive at second or third month of treatment
- (6) Relapses and returns after default
- (7) Exposure to institutions with MDR-TB populations or outbreaks (e.g. prisons)
- (8) Living in areas with high MDR-TB prevalence
- (9) History of using anti-TB drugs of poor or unknown quality
- (10) Treatment in programmes that operate poorly (especially drug stock-outs)
- (11) Co-morbid conditions associated with malabsorption
- (12) HIV in some settings

*Category II: World Health Organization (WHO) standard treatment for previously treated patients. **Category I: WHO standard treatment for new patients.

Adapted from Monedero and Caminero Luna [2009], Faustini *et al.* [2006], WHO [2004, 2008b].

with RIF and INH. MDR diagnose can, therefore, only be based on a bacteriological assessment.

The most common way to determine resistance is specimen culture and subsequently to confront the bacilli with different antibiotics, known as drug sensitivity testing (DST). DST can be performed in solid or more rapid liquid culture media. These types of techniques are still considered the gold standard. Nevertheless, DST in either modality presents important limitations [Kim *et al.* 2004]. Firstly testing could take from 10 days to 2 months, which for clinical purposes and decision making is clearly too long. In many instances, this period is frequently subject to further delays due to information, logistical and resource deficiencies [Yagui *et al.* 2006; Caminero Luna 2004]. Secondly, DST is a difficult and expensive technique. Regular DST should be performed only at quality-assured laboratories with safe facilities. Finally, *in vitro* DST often shows poor inter-laboratory reproducibility and low correlation with clinical response. *In vitro* and *in vivo* correlation is not optimal, especially for SLDs [Kim *et al.* 2004]. Fortunately, INH and RMP give the most reliable results [Caminero, 2005, 2006; Kim, 2005].

To complement the information given by DST, a complete history of the anti-TB drugs used by the patient and their availability in the country is needed. This is particularly relevant as the use of an anti-TB drug monotherapy for more than 1 month is thought to be one of the main predictors of resistance [Caminero, 2005, 2006; Kim, 2005].

To solve these disadvantages, new genotypic techniques are being designed. Fundamentally, these techniques identify mutations linked to phenotypic resistance. For instance, *rpoB* gene mutation is responsible for 95% of RIF resistance [Telenti *et al.* 1993]. The main advantage of genotypic DST is that it provides results in under 24 hours. In addition, it is relatively cheap and identifies resistance with a high level of reliability [Richter *et al.* 2009]. RIF resistance itself is a strong indicator of MDR, especially in patients previously treated for TB [Aziz *et al.* 2006; Skenders *et al.* 2005]. With knowledge of RIF status, an appropriate treatment can be rapidly identified, improving a patient's prognosis, avoiding amplification and interrupting MDR-TB transmission [WHO, 2008b]. These innovative methods have the potential to change practices in the treatment of MDR-TB.

Current evidence supports these findings [Barnard *et al.* 2008; Miotto *et al.* 2008]. As an example, in a busy TB clinic in South Africa, genotypic DST was tested under routine conditions. The study obtained high sensitivity (98.8%), specificity (100%) and positive (100%) and negative (99.7%) predictive values for MDR detection compared with conventional procedures. However, results for INH are not very sensitive as resistance can be linked to many different mutations [Richter *et al.* 2009].

Rapid testing, not only for INH and RIF, but also for ethambutol, FQ and second-line injectable resistance mutations, is available and currently under research. Initial publications on this issue reveal a high level of agreement with reference techniques, at least for FQ and injectables

[Hillemann *et al.* 2009]. By the time all gene mutations linked to resistance are identified and techniques are standardized, genotypic DST will probably be the best practice, due to its accuracy, reliability, quick results and cost effectiveness. Nevertheless, good quality and proficient laboratories are needed to perform genotypic DST, which could be a barrier for high burden countries.

Focusing on high burden LMICs, novel culture-based DST techniques are being developed and have been demonstrated to be highly cost effective. Principally these are the nitrate-reduction assay and the microscopic observation drug-susceptibility assay (MODS), which have obtained good results in several studies with regard to accuracy, sensitivity and specificity [Richter *et al.* 2009]. These are noncommercial and cheap laboratory techniques. However, relevant work on standardization and biosafety validation remains to be performed.

Approach to treatment

On the whole, either from a clinical or public health perspective, managing MDR-TB requires the application of the same principles as those for an susceptible TB. There are two main requirements for an effective TB treatment: multiple drugs to avoid further resistance and lengthy treatments to kill dormant forms and thus avoid relapses [Caminero, 2005]. Find in Table 3 the main aspects for correct MDR-TB management. Consequently, management of MDR/XDR-TB is long lasting and complicated. Experienced staff should take responsibility for these cases. However, given the high number of cases in LMICs, it is unrealistic for only specialists to treat such cases. Thus a standardized management approach is necessary [Caminero, 2005, 2006; Caminero Luna, 2004]. Standardized SLD regimens are fully appropriate if the MDR-TB patient has received only FLDs in the past. On the other hand, if the patient received FLDs and SLDs, an individualized SLD regimen could be more appropriate.

As mentioned above, TB is one of the most neglected diseases in terms of research and development. This is especially true for MDR-TB. In fact there are probably more contradictions than evidence [Caminero, 2006]. Randomized controlled trials (RCTs) on which the main clinical and control measures should be based should be simply nonexistent. In fact, the vast majority of

research knowledge was obtained from INH-resistant TB studies carried out during the 1950s and 1960s prior to the discovery of RIF and FQs. However, once a patient is diagnosed with MDR/XDR-TB, a treatment schedule based on the following logical steps, or similar, should be followed [Monedero and Caminero Luna, 2009; Caminero, 2006].

Step 1. Selection of number of drugs

To cure and avoid resistance amplification, a patient requires a treatment based on new and effective drugs. This relates to the application of anti-TB drugs that have not previously been applied in real or masked monotherapy or with effectiveness assured by DST. From a bacteriological perspective, three new and effective drugs would be sufficient to cure and avoid amplification. However, in the field, not infrequently the effectiveness of the drugs is compromised, especially with SLDs that have a reduced capacity to reach high tissue concentrations and have weak bacteriostatic activity [Caminero, 2006]. Thus, at least four new and effective drugs are necessary to remove all probability of amplification [WHO, 2008b; Caminero, 2006]. Once a patient has MDR-TB, in many setting the only available SLD schedule represent the very last chance of cure. Hence, treatment should not be started until four effective drugs are available for the whole duration of the treatment.

Step 2. Drugs to use

Not all anti-TB drugs have the same effectiveness and toxicity and thus are classified into five different groups [WHO, 2008b; Caminero, 2006] (see Table 2). A rational way to select use is to employ drugs from the most powerful and least toxic to the least powerful and most toxic. For instance, to use as many drugs as possible from group 1 (FLDs), only one drug from group 2 (FQ), only one drug from the group 3 (injectables) and whatever else is needed until reaching four effective drugs from group 4 (toxic and low activity drugs). Finally, use group 5 drugs (low evidence or very low activity) if four effective drugs were not reached with the previous groups. Nevertheless, being very low activity drugs, use 2 group 5 drugs every time you need one extra effective drug.

There is significant controversy on the role of FLDs in MDR/XDR-TB treatment, including high dosages of INH. A recent RCT has demonstrated quicker smear negativation in MDR cases with same side effect profile [Katiyar *et al.* 2008]. Different mutations are linked to INH resistance

Table 2. Rational classification of antituberculosis drugs.

Grouping	Drugs
Group 1: first-line oral agents	isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z)
Group 2: injectable agents	kanamycin (Km); amikacin (Am); capreomycin (Cm); streptomycin (S)
Group 3: fluoroquinolones	ofloxacin (Ofx); moxifloxacin (Mfx); levofloxacin (Lfx)
Group 4: oral bacteriostatic second-line agents	ethionamide (Eto); prothionamide (Pto); cycloserine (Cs); terizidone (Trd); p-aminosalicylic acid (PAS)
Group 5: agents with unclear efficacy	clofazimine (Cfz); linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H); clarithromycin (Clr)

Adapted from: Monedero and Caminero Luna [2009], WHO [2008b], Caminero [2006].

Table 3. Fundamental aspects of multidrug-resistant tuberculosis management.

Steps	Considerations
1. Diagnose	Confront information History of drugs: 1 month of monotherapy or single drug intake over a failure regimen could be a strong predictor of resistance. DST: most reliable for R and I; also reliable for Km and FQ; less reliable for E and P; very low reliability for group 4 drugs.
2. Number of drugs	'At least four effective drugs': never used in the past or susceptible by DST taking into account DST reliability and cross-resistance.
3. Drug selection	Use FLDs if still effective. One injectable. One FQ. Use group 4 drugs until complete four effective drugs. If necessary, use group 5 drugs to strengthen the regimen or when four effective drugs are not reached with the previous groups.
4. Length of the injectable	At least 4 months after smear or culture conversion. Longer if there is not three effective drugs during the continuation phase or drugs 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 with a multidrug-resistant patient who was treated with them (treat with the effective regimen of the index case).

DST, drug sensitivity test; E, ethambutol; FLD, first-line drugs; FQ, fluoroquinolone; I, isoniazid; Km, kanamycin; P, pyrazinamide; R, rifampicin; SLDs, second-line drugs.
Adapted from: Monedero and Caminero Luna [2009], WHO [2008b], Caminero [2006].

and cross resistance with ethionamide through an intricate process. It is becoming clear that a high INH dosage could play a relevant role in MDR treatment [Schaaf *et al.* 2009; Van Deun *et al.* 2004]. In addition, there is a lack of consensus regarding the role of other FLDs such as pyrazinamide (Z) and ethambutol (E) on MDR/XDR-TB, especially taking into account that their DST is not very reliable. Nonetheless, some articles have reported good outcomes in patients using Z and E when they have susceptible DST [Migliori *et al.* 2007; Mitnick *et al.* 2003]. Thus, it is probably justified to include these drugs in the MDR/XDR-TB treatment when the DST demonstrates susceptibility. However, they should not be counted as part of

the four new effective drugs as they had been administered for more than 1 month in a treatment that did not cure the patient.

Only one FQ should be used, given that all FQs have the same phenotypic target. Hence, no benefit is achieved by adding more than one while toxicity and cost are increased. The same reasoning applies to second-line injectables. With reference to cross resistance, it is important to consider that old generation FQs probably have complete cross resistance with other FQs of the same generation, but not with other newer FQ. This is particularly important for ofloxacin (Ofx), the FQ most frequently used to date.

Its resistance added to injectable resistance defines XDR-TB, but with the limited evidence available it is probable that 50% of Ofx-resistant cases are still susceptible to levofloxacin (Lfx) and moxifloxacin (Mfx) [Kam *et al.* 2006; Cheng *et al.* 2004]. There are clinical experiences reporting good outcomes with Lfx even in proven Ofx-resistant patients [Yew *et al.* 2003].

Another key issue is an awareness of the best FQ to use in MDR/XDR-TB patients. After a major review it is commonly accepted that ciprofloxacin is a very weak drug in TB and should no longer be recommended in MDR-TB management [Ziganshina and Squire, 2008]. Evidence is scarce regarding other FQ generations as the previous study is the only one that compared Ofx and Lfx in MDR patients [Yew *et al.* 2003]. Results were clearly in favour of Lfx. Given the lack of RCTs, there are two pharmacodynamic and pharmacokinetic studies comparing several FQs *in vitro* [Peloquin *et al.* 2008; Johnson *et al.* 2006], which have reported the best effectiveness surrogate parameters to high dosage Lfx (1000 mg). This is superior even to Mfx. Probably in terms of cost effectiveness the best drug to use is Lfx at 750–1000 mg per day.

The initial approach with regard to injectables is unclear. Probably, according to the limited literature available, the best choice of injectable in terms of cross resistance and toxicity could be the following sequence: capreomycin, then kanamycin and finally amikacin [Tsukamura and Mizuno, 1980; Tsukamura, 1969]; however, capreomycin is usually very expensive and difficult to acquire. Streptomycin is no longer recommended in MDR treatment mainly due to worldwide high levels of primary resistance and linked INH resistance [WHO, 2004, 2008b].

Step 3. Length of injectable treatment (intensive and continuation phases)

Basically, the difference between the intensive and continuation phases is injectable use. Together with FQs, injectables are the most powerful drugs for use in MDR-TB, although the longer they are used, the higher the toxicity becomes. In theory, it is safe to suspend the injectable and pass to the continuation phase when the bacilli burden has been reduced to an almost undetectable level. This occurs when the microscopic observations are negative and specifically when there are two negative microscopic observations with 1 month in between.

However, in the field, a more prudent approach is recommended to preserve the effectiveness of the continuation phase: retain the injectable for at least 6 months and at least 4 months after negative culture [WHO, 2008b]. In this way, the cure is maximized and resistance amplification probabilities are minimized. The injectable can be withdrawn safely only when at least three effective drugs remain in the regimen. Lengthy treatments with injectables should be considered if fewer than three effective drugs remain in the continuation phase or are very weak drugs [Caminero, 2006]. This could be relevant in XDR management where if the injectable is withdrawn, the remaining treatment schedule is weak. The risk of resistance amplification exists on a weak continuation treatment schedule. In such cases long injectable treatments of 6, 12 or even 18 months are to be assumed. Intermittent therapy (three times a week) can be considered in very long treatments or where there is a high risk of toxicity [WHO, 2008b]. When smears and cultures turn negative, the bacillary load is notably reduced. After two negative cultures or smears separated by 1 month, the intensive phase of treatment can be stopped. The continuation phase without injectables ought to last for 18 months.

Step 4. Surgery

The role of the surgery in MDR-TB is limited to exceptional circumstances [WHO, 2008b; Caminero, 2006]. These are mainly cases with fewer than four effective drugs available for their schedule (mostly XDR), if lesions are isolated and localized and where there is sufficient respiratory reserve [WHO, 2008b; Caminero, 2006]. The appropriate selection of candidates was the key factor for good performance in the only study carried out in LMICs [Somocurcio *et al.* 2007]; however, morbidity and mortality were often considerable.

Special cases

Given that the evidence for standard cases is limited, the approach for special cases is particularly controversial. At the moment the same rules as for adults are applied to children [WHO, 2008b]. Apparently children have lower levels of side effects with SLDs. Many professionals have significant doubts about use of FQs in children, but current evidence has proved that FQs were safe in more than 7000 cases [Burkhardt *et al.* 1997].

Special consideration should be given to pregnant women. Nowadays, the best practice is to avoid pregnancy during TB disease, but if this occurs, ideally MDR treatment should be delayed until after the second trimester. Injectables have proven to be teratogenic drugs and doubts remain about thioamides (ethionamide and prothionamide). If possible, both groups should be avoided. If there is no other option, the best recommendation is to use capreomycin out of the injectables because of its lower teratogenic profile [WHO, 2008b].

Little information is available regarding comorbidity conditions common to MDR-TB such as diabetes mellitus. However, some publications have reported worse outcomes and greater rates of relapse [Bashar *et al.* 2001]. Concerning MDR-TB and HIV, there are contradictory opinions as regards additive toxicities, malnutrition and other critical comorbidities. Probably the most controversial issues concern when to start antiretroviral therapy, how best manage (IRIS) and prevent immune reconstitution syndrome. There is as well a great lack of knowledge, for instance concerning drug to drug interaction while funding is very limited for these programmes in LMICs [Harries *et al.* 2009; Scano *et al.* 2008]. However, more is starting to become known about the interactions between SLDs and antiretroviral agents [Coyne *et al.* 2009], and it is expected that some of these questions will be answered in the near future.

In the case of new TB patients being MDR close contacts, treatment should be based on the same pattern of bacilli resistance of the index case if known, or on the effective regimen given to the former [Caminero, 2006]. Amendments can be made after DST results in case of susceptibility.

One important and unresolved issue is what to do with MDR-infected contacts (latent TB infection). Once again, evidence is limited to expert opinions [Fraser *et al.* 2006]. This could be crucial in HIV HBCs. To date there is no approved chemoprophylaxis schedule for contacts and the current recommendation is to be under close supervision [WHO, 2008b].

No clear guidelines exist for XDR cases since no RCTs are available. In addition, XDR conditions can be quite different from patient to patient depending on the pattern of resistance and previous drugs used. As well as issues relating to the

patient, the TB programme, resources, availability of drugs and social support prognosis will have an impact. In fact there are settings where XDR cases have obtained similar cure rates than MDR cases. Conversely, in other settings, XDR cure rates were extraordinary low [Sotgiu *et al.* 2009]. As a common approach, previous guidance for MDR diagnosis and treatment is suitable to perform diagnose and treatment for XDR cases. However, in XDR management, as four effective drugs are often not available, the use of multiple drugs (more than 6–8 in some settings), lengthy treatments (often more than 24–30 months), lengthy injectable use, surgery and others have to be considered [Sotgiu *et al.* 2009; WHO, 2008b].

Other key tools for MDR-TB success

Something that might seem obvious, yet is crucial, is the presence of a strong TB programme. It is thought that introduction of an MDR component into a weak Tuberculosis Directly Observed Treatment Short-course (DOTS) programme could quickly lead to the development of XDR with decreasing effectiveness of the susceptible TB programme [Sterling *et al.* 2003]. Clinical experiences and mathematical models conclude that poor treatments paradoxically are worse than no treatment. A narrow focus on MDR-TB therapy could make a bad situation worse by increasing the number and pattern of resistance of circulating strains in the community [Coker, 2004; Pablos-Mendez *et al.* 2002].

Without an integrated programme structure, all the approaches mentioned here are likely to fail. The DOTS strategy is at present the best framework for managing susceptible and resistant TB. Without a good DOTS framework, failures, defaults and drug shortages are more likely to occur. At the same time MDR committees comprising laboratory staff, pharmacists, clinicians and social workers are needed to increase the chances of success [Nathanson *et al.* 2004], improve decision making and ensure a coordinated approach. On the other hand, strong side effect management is needed since many of the SLDs have a toxic profile. Ancillary drugs need to be easily available. In addition, to avoid defaults, regular monitoring visits with basic clinical blood tests, and treatment support are required and ancillary drugs need to be easily available [WHO, 2008b].

At the same time, having a strong DOTS programme limits the creation of new MDR cases. Actions to limit the creation of MDR cases under

programme conditions are essential [Caminero, 2008]. For instance, in the case of an intermittent continuation phase, adherence to the maximum and assuring at least three intakes per week is necessary. Other basic practices to avert MDR is the use of anti-TB fixed-dose combinations, and extend the intensive phase by 1 month in the case of smear positivity at the end of the second month [Caminero, 2008].

Another key tool in limiting the burden of MDR/XDR-TB is the use of infection control measures. The importance of infection control was highlighted after the Tugela Ferry deadly XDR outbreak among HIV-positive patients [Gandhi *et al.* 2006]. It was discovered that most of the cases were infected at health facilities. In fact, not all hospitals are prepared to admit MDR/XDR cases. In many settings the most simple, essential and effective administrative infection control measures are not followed [WHO, 2009d]. In terms of risk reduction, simply separating the MDR/XDR patients into a different room, which is well ventilated and has natural light, can make a vast difference [Bock *et al.* 2007].

Finally, it is important to mention that TB, and especially MDR-TB, is more than a clinical problem. Programmes have to deal with patients with social difficulties and poverty [Atre and Mistry, 2005; Yong Kim *et al.* 2005]. Behind an MDR patient, there is always a sad story. Clinicians should open their minds to social diseases and social solutions. Supportive nurses, counsellors and social workers play a relevant role in MDR-TB [Farmer *et al.* 1998]. Economic aid and food support as well as comprehensive and psychosocial approaches are strongly linked to positive outcomes in these lengthy and toxic treatments [Mitnick *et al.* 2008; WHO, 2008b]. It makes no sense to spend thousands of dollars on an expensive drug cocktail if the patient defaults because of hunger. Unfortunately, this tends to happen in many MDR programmes all around the world.

Promising approaches and tools

Concerning current drugs, an important issue to solve is the role of new generation FQs such as gatifloxacin and Mfx. If these have a similar sterilizing activity to RIF it should be possible to shorten MDR treatments. Ongoing RCTs will provide answers to some of these questions in the near future.

Another promising approach, as previously mentioned, is the use of high dosages of INH, which

proved effective in an RCT on MDR-TB [Katiyar *et al.* 2008]. In another study, a treatment using a schedule of high INH dosages and clofazimine demonstrated optimal cure results [Van Deun *et al.* 2004]. Clofazimine could be a relevant MDR drug in the near future according to clinical experiences, although to date, limited published evidence is available.

Linezolid (Lzd) a group 5 drug, could be a potential tool, especially in XDR-TB treatment [Condos *et al.* 2008; Ntziora and Falagas, 2007]. More evidence of its benefits is emerging, especially when used in lower and safer dosages [Migliori *et al.* 2009; Park *et al.* 2006]. Lzd is suitable for XDR and MDR cases, but its use should probably be limited to severe cases, for example, those resistant to more than seven drugs [Migliori *et al.* 2009]. However, Lzd has only proved so far to have poor bactericidal activity [Dietze *et al.* 2008]. In addition, due to its price and toxicity profile (lactic acidosis and optic or peripheral neuropathy and others) [De Vriese *et al.* 2006], it is not a suitable drug for most LMICs, where the majority of MDR cases exist.

There are several drugs emerging with innovative actions [Coyne *et al.* 2009; Van Den Boogaard *et al.* 2009], which could transform the MDR landscape in the future. New Rifamycins, such as rifalazil, have had good preliminary results. New family drugs such as diarylquinolines have demonstrated early bactericidal activity against susceptible and MDR-TB. From these, the component TMC207 is one of the most promising future TB drugs [Diacon *et al.* 2009]. Nitroimidazoles, another new class of drugs, have candidate molecules such as PA-824 and OPC-67683, which have demonstrated potent activity against active and dormant forms. Others compounds such as SQ109 and nitrofuranyl amides have demonstrated activity *in vitro* [O'Brien and Spigelman, 2005]. Nevertheless these and other molecules are unlikely to be ready at an affordable price for clinical use in LMICs in the next 10–15 years [Monedero and Caminero Luna, 2009].

Significant efforts have been made towards a vaccination, which would probably be the best tool for tackling TB. Likewise, this scenario would take no less than 10–20 years to be introduced into LMICs. In 2010, taking into account the delays in the introduction of new solutions, probably the wisest approach in TB and MDR-TB

management is to optimize the current tools through low-cost and low-risk policies such as those mentioned in this paper to prevent an increase in drug resistance and, once it has appeared, to improve its management [Monedero and Caminero Luna, 2009].

Conflict of interest statement

The authors declare that there is no conflict of interest.

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