Tuberculosis: are we making it incurable?

José A. Caminero[1,2], Alberto Matteelli[3] and Robert Loddenkemper[4]

Affiliations: [1]Dept of Pneumology, Universitary Hospital of Gran Canaria ''Dr. Negrín'', Las Palmas de Gran Canaria, Spain. [2]International Union Against Tuberculosis and Lung Disease (The Union), Paris, France. [3]Institute of Infectious and Tropical Diseases, University of Brescia, Brescia, Italy. [4]German Central Committee against Tuberculosis (DZK), Berlin, Germany.

Correspondence: J.A. Caminero, Dept of Pneumology, Universitary Hospital of Gran Canaria ''Dr. Negrín'', Barranco de la Ballena s/n, 35010 Las Palmas de Gran Canaria, Spain. E-mail: jcamlun@gobiernodecanarias.org

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With proper management all TB patients have a chance to be cured; it should never be thought that a TB case is incurable http://ow.ly/ksm5g

Tuberculosis (TB) is most probably the disease that has caused more damage to the human species throughout its history in terms of number of patients and, above all, death toll. There have been thousands of years spent fighting against *Mycobacterium tuberculosis* in which the human species could only rely on the efficiency of the immune system [1]. We must recall its importance as, in the pre-antibiotic era, the immune system alone could ensure important achievements such as: 1) only 50% of the people exposed to *M. tuberculosis* contract the infection [2]); 2) only 10% of those infected progress to active disease; and 3) up to 30% of patients with advanced TB disease heal spontaneously (fig. 1) [3, 4]. In spite of this, the fate of TB patients in the pre-chemotherapy period was very bleak, with a mortality of >50% within 5 years after the onset of disease [3, 4]. For centuries, several empirical treatments were attempted to trying to change this fateful prognosis. Additionally, sanatoriums were built throughout the world for many decades (fig. 2). However, all these interventions were not really effective, and none of them contributed significantly to improve the doom of TB patients [4]. Then, fortunately, their fate changed dramatically with the advent of the antibiotic era. The two decades from the discovery of streptomycin in 1943 to that of rifampicin in 1963 changed a devastating disease into a relatively easy to cure one. Not only were up to 11 different drugs with activity against *M. tuberculosis* discovered (streptomycin, p-aminosalicylate (PAS), thiacetazone, isoniazid (H), pyrazinamide, cycloserine, kanamycin, ethionamide, ethambutol, capreomycin and rifampicin (R)), but, based on multiple randomised clinical trials, the basic fundamentals of TB treatment were also established [4, 5]. Probably the most essential of these was the need to combine at least two to three drugs to which the patient was sensitive, as *M. tuberculosis* can develop resistance to single drugs.

The ability of *M. tuberculosis* to develop resistances to antibiotics was described in the very first randomised clinical trial conducted with streptomycin and published in 1948 [6]. The first great lesson learnt from early randomised clinical trials was that using TB drugs in monotherapy, or in poor combinations, would lead to the selection of resistance to these drugs [5]. Thus, as a result of the misuse of the available drugs, mono-resistant TB started to develop, followed by poly-resistant TB (resistance to two or more drugs), multi-drug resistant (MDR)-TB (resistance to at least H+R), and extensively-drug resistant (XDR)-TB (defined as MDR-TB plus resistance to at least one fluoroquinolone (FQ) and one second-line injectable drug). The need for definitions beyond XDR-TB is a currently an issue of debate.

The definitions in the field of anti-TB drug resistance should be based on two main factors: 1) the capacity to reliably test anti-TB drugs in the laboratory, and 2) the possible different prognosis that a new definition could bear. As is well known, rifampicin is currently by far the best available drug, and is the only one that combines excellent bactericidal, sterilising and resistance preventing activity [7]. Therefore, it is the only drug with the ability to reduce the duration of TB treatment to 9 months (6 months if the other highly

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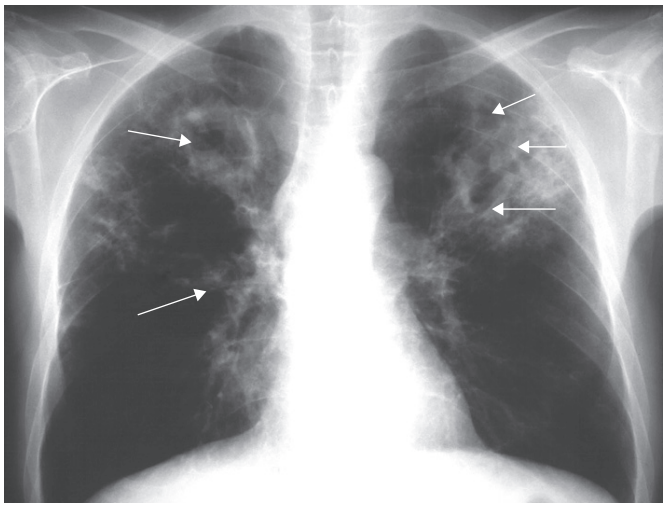

FIGURE 1 Chest radiograph showing extensive cavitary tuberculosis (arrows).

sterilising drug, pyrazinamide (Z) is included) [5]. The lack of R in a regimen not only requires the extension of the treatment duration to a minimum of 12–18 months, but also clearly worsens the prognosis of the patient [4]. In addition, the clinical reliability of drug susceptibility testing for R is very high. Thus, resistance to R is the basis of the currently accepted definition of MDR-TB, although, little by little, more people are supporting the view that even mono- or poly-resistance to R with *in vitro* susceptibility to H (which is very uncommon) should be accepted as the definition of MDR-TB. The achievable treatment success rate for MDR-TB cases ranges between 62% and 69% using long and poorly tolerated second-line drug regimens [8, 9]. These success rates can be achieved despite the absence of R and H in the regimen because we have two other families of drugs with high efficacy against *M. tuberculosis*: the FQs and the second-line drug injectables (kanamycin, amikacin and capreomycin) [7], both with reproducible and relatively reliable drug susceptibility tests. Therefore, the definition of XDR-TB covers these two families of drugs, which can be tested in the laboratory and whose resistance carries a clearly worse prognosis, with a success rate of just 43.7% as reported in the meta-analysis by JACOBSON *et al.* [10]. There is convincing evidence that FQs are associated with a better prognosis when used for the treatment of MDR-TB [9, 11, 12]. Interestingly, the meta-analysis carried out by JACOBSON *et al.* [10] showed that a success rate of 59% could be reached in those settings where a later generation FQ was systematically used to treat XDR-TB strains which, by definition, are resistant to FQs.

This issue of the *European Respiratory Journal* contains two important articles that shed light on the diversity of the prognosis of patients with strains with MDR-TB and beyond. The first article by FALZON *et al.* [13] analyses the outcome of patients with a gradient of resistance from MDR-TB (without additional resistances) to XDR-TB. In the second article MIGLIORI *et al.* [14] discuss the appropriateness of adopting a

FIGURE 2 A photograph showing a sanatorium, which were built with large patios where tuberculosis patients could rest.

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definition beyond XDR-TB, based on the worse prognosis found when the resistance pattern extends, especially to all second-line drug injectables.

The most important finding in the article by FALZON *et al.* [13] is that, among the two drug families that constitute the treatment backbone for patients with MDR-TB, FQs, especially the later generation ones, are better than second-line drug injectables. The treatment success rate (compared to treatment failure, relapse and death) among almost 7000 MDR-TB patients from 26 experienced centres was progressively decreasing from 64% for patients with MDR-TB without additional resistance, to 56% for MDR-TB with additional resistance to second-line drug injectables only, to 48% for MDR-TB with additional resistance to FQs only, and to 40% for XDR-TB patients. Remarkably, this poor outcome of 40% for XDR-TB patients is very close to the 43% published by JACOBSON *et al.* [10].

The findings of FALZON *et al.* [13] suggest that the XDR-TB definition adopted in 2006 [15] may not be the most appropriate one, because, for instance, patients with MDR-TB with resistance to ofloxacin and kanamycin alone (by definition XDR-TB cases, although the strain can be susceptible to all other first-line drugs, to a later generation FQ and to other second-line drug injectables such as capreomycin) have a prognosis which is closer to that of MDR-TB than XDR-TB [16]. Following this reasoning, the correct definition of XDR-TB should probably cover all first-line drugs (not only H and R), plus all FQs and all second-line drug injectables [17].

The data published by MIGLIORI *et al.* [14] in this issue support this hypothesis. Their data show that among patients with XDR-TB (405 in total), the poor prognosis of those without further resistance (n=301, treatment success 43%) is worsened by the addition of resistance to all second-line drug injectables (n=68, treatment success 34%), and made worse further by the addition of resistance to ethambutol and/or pyrazinamide (n=42, treatment success 19%). Interestingly, prognosis was not affected by resistance to any of the group 4 drugs (ethionamide/prothionamide, cycloserine/terizidone or PAS) in the presence of resistance to all second-line drug injectables. These results are slightly in contrast to the published findings of a recent meta-analysis including the largest number of MDR-TB patients published to date, in which, in addition to FQs, the possibility of using ethionamide/prothionamide was associated with a better prognosis [18].

The article by FALZON *et al.* [13] provides additional important original information. First, it reports that, contrary to the case of MDR-TB which requires an ideal number of four drugs for effective treatment [19, 20], in the case of XDR-TB the use of at least six drugs in the intensive phase is associated with a better treatment success. Secondly, it suggests that the duration of treatment recommended for MDR-TB is also appropriate to treat XDR-TB [19].

The conclusions reached by MIGLIORI *et al.* [14] are important. The authors admit that, in spite of the evidence that the current XDR-TB definition may not be the best to predict the outcome of affected patients, limitations in availability, accuracy and reproducibility of current drug susceptibility methods preclude the adoption of a useful definition beyond the one currently used for XDR-TB. We agree with this statement, although, perhaps, the current definition of XDR-TB could be revised in order to include all first-line oral drugs (MDR-TB+ethambutol+pyrazinamide), all FQs and all second-line drug injectables [17].

In summary, it seems that the chance of cure for patients with XDR-TB plus resistance to all second-line drug injectables is practically the same as for patients with cavitary TB not receiving any treatment in the pre-antibiotic era [3]. Moreover, the chance of cure for patients with XDR-TB without widespread resistance (treatment success 40–43%) is slightly better than the spontaneous healing produced by the action of our immune system. It is of interest to note that, in order to reach a relatively poor treatment outcome, very lengthy toxic and expensive regimens have to be used. The low cure rate for XDR-TB is surprising, in light of the evidence from the pre-rifampicin and pre-FQ studies, as most TB patients with resistance to streptomycin plus PAS plus isoniazid (who were very similar to current XDR-TB cases) were cured when combining only three drugs to which the patient was sensitive [21–24]. The reasons for such discrepancies are unclear: the older findings were all derived from a very individualised management in selective referral centres, and indirect evidence that treatment of TB, even in patients with a very extensive pattern of resistance (beyond XDR-TB), is positively affected by the adoption of the best available standard of care. The high chances of cure recently published for patients with XDR-TB support this view [25]. Still, it is worrisome and worth noting that the clinical centres contributing cases to the series analysed by both FALZON *et al.* [13] and MIGLIORI *et al.* [14] represent centres of excellence: a warning not to surrender to complacency when dealing with XDR-TB.

Many mistakes in the use of anti-TB drugs have led to the current situation with an increasing number of TB patients carrying strains with a very extensive pattern of resistance. What is even worse is that patients with TB with widespread resistance still suffer many clinical (*e.g.* addition of only one to two drugs to a

failing regimen, or irrational use of available effective anti-TB drugs) or programmatic (no social support, no good approach to potential adverse drug reactions, no good adherence supporting initiatives, *etc.*) errors [26, 27]. If this trend is not reversed, the chances of cure for TB patients will remain low, and the high costs of treating MDR- or XDR-TB may become unaffordable in low-income countries [28].

One final remark, even considering the clear evidence that the prognosis of TB patients worsens when the pattern of resistance increases, it should never be accepted that a TB case is incurable. All TB patients, even those with XDR-TB or beyond XDR-TB, should always have a chance to be treated using the available clinical and programmatic management strategies. The arrival of new drugs [29] will certainly enhance our capacity to cure TB patient, if we are able to protect them from the ability of *M. tuberculosis* to generate resistance [19, 20], and will ensure their durability to a time range similar to the very long one elapsing from the discovery of a new compound to its registration for the market use.

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