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Editorial

Do we need a new Fleming époque: The nightmare of drug-resistant tuberculosis

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ABSTRACT

Tuberculosis represents an important clinical and public health problem globally, particularly in low- and middle-income countries. During the last 20 years, two relevant events has changed the epidemiology of the disease: the spread of the TB/HIV co-infection and the emergence and spread of the multi-drug resistance tuberculosis (i.e., tuberculosis caused by strains resistant to at least isoniazid and rifampicin). The latter phenomenon has been generated by the inappropriate management of the anti-tuberculosis drugs. Currently, the World Health Organization estimates at least 600,000 MDR-TB cases worldwide, particularly in China, India, South Africa, and in former Soviet Union countries. Unfortunately, new difficult-to-treat MDR-TB cases have been described, named XDR- or TDR-TB (extensively or totally drug-resistant tuberculosis, respectively). Numerous observational retrospective studies proved the poorer prognostic profile of the MDR-TB cases when compared with drug-susceptible tuberculosis. The clinical management of the patients with an XDR and beyond pattern is complicated owing to the poorest, expensive, and toxic therapeutic options. MDR-TB is currently under-reported because of methodological issues, mainly related to the poor proficiency of laboratory testing. National public health strategies should reduce the increase of tuberculosis cases without therapeutic alternatives. Furthermore, research and development activities, based on continuous and sustained funding, should be improved, together with the implementation and the scale-up of effective infection control measures in healthcare settings and in the community.

Resistance to antibiotics is deemed a man-made phenomenon attributable to the selection of naturally resistant strains. It is mainly caused by a sub-therapeutic drug exposure related to an inadequate (drug/regimen selection/dosage and duration of treatment) antibiotic prescription [1–7].

This phenomenon, described for anti-viral, anti-bacterial, anti-protozoal, and anti-mycotic drugs, can have relevant clinical and public health consequences, particularly in an era where research and development activities of the pharmaceutical companies are focused mainly on chronic-degenerative diseases [8].

In the fight against some infectious diseases (for instance, those caused by *Staphylococcus aureus* or *Escherichia coli* infections), it was described as a sort of 'back to the future', that is, a return to a pre-Fleming period, where the natural history of the infectious diseases could not be altered [1,2].

Tuberculosis, one of the most important contagious diseases globally, is currently treated with a poli-chemotherapeutic approach whose efficacy and safety have been frequently argued, particularly in some high-risk groups. Since the 1950s, it was described as the mono- or poli-resistance of *Mycobacterium tuberculosis* isolates to anti-tuberculosis drugs, and several therapeutic options have been suggested [9,10]. However, since the 1990s, a new epidemiological scenario has been described with the emergence and spread of pulmonary and/or extra-pulmonary forms of multi-drug resistant tuberculosis, i.e. tuberculosis caused by strains resistant to at least two of the most effective anti-tuberculosis drugs: isoniazid and rifampicin [11–15].

Since its first description, it was clear its poorer prognosis if compared with drug-susceptible tuberculosis and the necessity to have more efficacious and safer pharmacological alternatives [11,16–19].

However, the most impressive burden of the MDR-TB was mainly located in low- and middle-income countries, where the political, healthcare, and societal roots of this new epidemiological entity could not be hindered. In 2006 a new, more serious, resistance pattern was depicted and named extensively drug-resistant tuberculosis (XDR-TB, that is an MDR-TB with additional resistances to any fluoroquinolones and to at least one second-line injectable-amikacin, capreomycin, or kanamycin). Numerous manuscripts and systematic reviews summarized its striking negative impact on clinical outcomes like mortality, treatment success and failure [20–23]. The recent World Health Organization global report, issued in 2012, pointed out that there were 27 high MDR-TB burden countries in 2011, with the highest absolute frequencies in China, India, Russian Federation, and South Africa, which represent 60% of the total cases. The highest proportions of new and previously treated MDR-TB patients were noted in Eastern Europe and Central Asia. MDR- and XDR-TB have been reported in 135 and 84 countries, respectively, with a best estimated size of 630,000 cases [24].

In 2007 Migliori et al. described the first two cases of tuberculosis patients without therapeutic options, because of resistances against first-, second-, and third-line drugs; they used for the first time the term XXDR for extremely drug-resistant tuberculosis [25]. Small samples of patients with similar drug resistance patterns were described in Iran and India and were named totally drug-resistant tuberculosis (TDR-TB) [26–28].

Actually, there is no agreed-upon definition for cases of tuberculosis with resistances to all the anti-tuberculosis drug armamentarium. If the acronyms M/XDR-TB were universally accepted because of a standardized methodology of the *in vitro* susceptibility testing for the case-defining drugs, the World Health Organization does not give full confidence to the laboratory evaluation for some of the second- and third-line drugs. What was proven by a retrospective collection of several cohorts worldwide is the clinical and operational/public health value of a resistance pattern more complicated than XDR, having a higher risk of treatment failure and death, as well as a lower likelihood of treatment success, with more possibilities of *M. tuberculosis* transmission [29,30]. These forms of disease mimic the natural history of the untreated tuberculosis, evoking the above-mentioned paradigm of "Drug resistance beyond XDR-TB: back to the future" [31].

The recent advertisement in the media of those drug-resistant forms could be dangerous for the tuberculosis patients: it should be scientifically driven in order to avoid new stigmas and racism-like episodes. On the other side, its knowledge could have a significant impact on the political world, pushing new public health strategies of continuous and relevant financing for the healthcare strengthening and antibiotic stewardship. The epidemiological burden is at this time relevant, but every political and scientific effort should be put in place by all the stakeholders to avoid a new dramatic epidemic which would mainly affect the poorest and most vulnerable human beings.

Conflict of interest

We have no conflict of interest to declare.

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