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Eur Respir J 2016; 47: 660–664 | DOI: 10.1183/13993003.01015-2015 | Copyright ©ERS 2016

Tuberculosis elimination, patients' lives and rational use of new drugs: revisited

To the Editor:

The World Health Organization (WHO) has recently published a framework on tuberculosis (TB) elimination opening debates on elimination and multidrug-resistant (MDR)-TB [1, 2]. The document highlights MDR-TB as a core area, emphasising the moral duty of preventing the selection of MDR-TB (by treating susceptible cases correctly with first-line drugs) and the necessary efforts to treat it when diagnosed. Unfortunately, treating MDR- and extensively drug-resistant (XDR)-TB is much more onerous, lengthy and terribly expensive; treatment outcomes remain suboptimal, adverse events being frequent and severe [3–6]. The availability of new drugs has offered new possibilities for saving patients who were not previously treatable and posed new challenges related to their rational use in order to prevent selection of resistant strains of *Mycobacterium tuberculosis* [7–10].

The aim of this report is to describe a patient's 22-year ordeal with TB. He was treated for two decades unsuccessfully until the advent of new active drugs. We hope that this case will serve as a scenario to emphasise the importance and moral obligations of physicians not to foster resistance, as well as to conserve new drugs for subsequent generations.

In the 1990s, the approach to the treatment of resistant TB differed greatly and was based on the second-line TB drugs available at the time, in an era preceding the development of specific guidelines [11], and before the availability of new "off-label" drugs (linezolid and imipenem).

The patient in question is a HIV-negative Italian man, who was 32 years of age at the time of MDR-TB diagnosis (March 1991). He had been previously treated for pulmonary nodular TB between 1985 and 1991. He had no known risk factors or contacts for TB. He was transferred to the MDR-TB reference hospital in Sondalo, Italy, in March 1991 when his condition deteriorated following retreatment with first-line drugs and ciprofloxacin (table 1), a single active drug added to a failing regimen.

On admission he was sputum smear positive (grade 4+) and culture positive (20 colonies in solid medium); he was resistant to all first-line drugs, *para*-aminosalicylic acid (PAS) and terizidone, with susceptibility to ofloxacin and capreomycin. The disease had progressed, with bilateral nodular infiltrates with cavities in the upper left lobe. The initial regimen included amikacin, clofazimine, ofloxacin and PAS; he also underwent bisegmentectomy of the left upper lobe in November 1991.

TABLE 1 Treatment history of a patient diagnosed with multidrug-resistant (MDR) tuberculosis (TB) in 1991, with available drugs till 2005, then with a salvage regimen approach, finally being cured after 707 days of hospital admission, surgery and administration of 15 different drugs

	Chest radiography	Resistance pattern on drug susceptibility test	Treatment	Sputum smear (grading)	Culture (colonies n)
When TB was probably susceptible to all drugs					
1985	Nodular monolateral lesions (upper left lung)	Not performed	H, R, E	Negative	Negative
1986	Cavity (upper left lung)	Not performed	H and R, then E and Cfx	Positive on bronchoaspirate	Positive
1991	Cavities (worsening)	Not performed	Transfer to Sondalo reference hospital	Not performed	Not performed
From MDR- to XDR-TB, treating with second-line anti-TB drugs available at the time					
March 1991	Bilateral lesions with cavities in the upper left lobe	H, R, S, E, PAS, Trd	12 drugs from March 1991 to July 2001: H, R, S, E, Amk, Cfx, Cfz, Clr, Eto, Ofx, PAS, Trd; bisegmentectomy at the upper left lobe in November 1991	Positive (4+)	Positive (20)
August 1992	Same as previous	+Km		Positive for the entire period	Positive for the entire period
October 1999	Same as previous	+Eto			
October 2000	Same as previous	+Z			
July 2001	Bilateral cavities	+Cfx			
When XDR-TB, with a salvage regimen comprising newly available off-label drugs					
March 2005 to August 2007	Bilateral cavities	H, R, S, E, Z, Cfx, Eto, Km, PAS, Trd	E, Mfx, Clr, Imi, Trd, Lzd,	Negative after 72 days	Negative after 127 days

First-line anti-TB drugs are as follows. Group 1 oral drugs: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), rifapentine and rifabutin. The second-line anti-TB drugs are as follows. Group 2 injectable aminoglycosides: streptomycin (S), kanamycin (Km) and amikacin (Amk); group 2 injectable polypeptides: capreomycin and viomycin. Group 3 oral and injectable fluoroquinolones: ciprofloxacin (Cfx), levofloxacin, moxifloxacin (Mfx), ofloxacin (Ofx) and gatifloxacin. Group 4 oral drugs: *para*-aminosalicylic acid (PAS), cycloserine, terizidone (Trd), ethionamide (Eto), prothionamide, thioacetazone and linezolid (Lzd). The third-line anti-TB drugs are as follows. Group 5: clofazimine, Lzd, amoxicillin plus clavulanate, imipenem (Imi) plus cilastatin and clarithromycin (Clr). XDR-TB: extensively drug-resistant.

During his treatment, the patient was admitted 24 times (664 days) between 1991 and 2005, remaining sputum smear and culture positive throughout, while adhering strictly to therapy. In August 1992 (10th admission), he developed resistance to kanamycin; in October 1999, to ethionamide; in October 2000, to pyrazinamide; and in July 2001, to ciprofloxacin. In November 2001 (24th admission), exhausted, he refused to be treated any further and was isolated in his home.

In March 2005, he was admitted in a critical condition (26th admission) with disseminated TB, a miliary pattern on chest radiography, epididymitis and Pott's disease, as well as sputum smear (4+) and culture positivity (200 colonies). However, the patient did manage to survive till new active and effective drugs became available.

A salvage regimen was initiated composed of linezolid (600 mg twice a day), imipenem (500 g four times a day), terizidone, ethambutol and clarithromycin. The first two drugs in the regimen were introduced in the TB armamentarium for salvage therapy in 2005 [12].

After 404 days of the salvage regimen, linezolid was stopped due to development of severe anaemia, while imipenem was interrupted after 428 days (hospital administered) without adverse events reported (28th admission); continuation-phase treatment continued with terizidone, ethambutol, clarithromycin and moxifloxacin. The latter was newly available and added despite ciprofloxacin resistance. The patient sputum smear converted 72 days and culture converted 127 days (table 1) after starting the salvage regimen.

At the end of August 2007, 29 months after commencing the salvage treatment with two unlicensed drugs in his optimised background regimen, the patient was declared cured according to the WHO definition [11]. As of today, the patient (who has since fathered two children) is well and has long since resumed a normal working life.

This patients' story, spanning three decades since his first diagnosis with TB, with a total of 707 days in hospital split into 29 hospital admissions, demonstrates the ease of developing MDR- and XDR-TB if initial treatment is not correctly managed. Unfortunately, at the time, many clinicians had relegated the emergence of resistance to streptomycin and isoniazid to the history books, and had forgotten the dangers of adding a single active drug to a failing regimen; the addition of ciprofloxacin to his failing regimen led to resistance and to a cascade effect endangering other agents in the second-line regimen (ethionamide and kanamycin), to which his TB later became resistant.

The causation of TB resistance is multiple and complex. MDR- and XDR-TB can be primary; caused by lack of adherence, drug quality or stock outs; iatrogenic; or related to bacillary burden. The patient was previously treated for TB and may have had resistance from three potential sources, namely primary infection with resistant bacilli, acquisition of resistance during treatment and re-infection with resistant bacilli. Adding single active drugs to a regimen, either through lack of experience or unknowingly from the unavailability of drug susceptibility, is a iatrogenic cause of MDR TB, which is avoidable.

This report highlights how limited treatment options were until recently, and how new drugs offer hope to patients and the importance of using them well. That being said, history runs the risk of repeating itself and we risk losing the precious few new drugs we have through lack of experience in their use. The importance of ensuring adequate treatment in specialised reference centres with infection control measures in place needs to be stressed.

Historically, this was, to our knowledge, the first patient to receive imipenem and linezolid in combination and off label for the treatment of MDR/XDR-TB [12]. Today, we salvage patients with either bedaquiline or delamanid; we are awaiting safety data for their combined use and hope that we will not select resistance to either of them beforehand [13, 14]. It is of utmost importance to use these latter drugs effectively if elimination is ever to be a reality and to stop history from repeating itself [15].

Although the MDR-TB burden is low in absolute terms in low TB incidence countries, similar cases sustained by resistant strains of *M. tuberculosis* are likely to be seen more frequently in the future. Europe needs to prepare itself to manage them correctly in order to reach elimination.

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The importance of not fostering resistance and conserving new TB drugs for subsequent generations
http://ow.ly/TkR8K

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Received: Aug 06 2015 | Accepted after revision: Sept 23 2015 | First published online: Nov 05 2015

Conflict of interest: None declared.

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Eur Respir J 2016; 47: 664–667 | DOI: 10.1183/13993003.01297-2015 |

Tuberculosis in Germany: a declining trend coming to an end?

To the Editor:

In the context of the newly adopted World Health Organization (WHO) End TB strategy, an action framework towards tuberculosis (TB) elimination in low incidence countries has been launched [1, 2]. Its aim is to reach pre-elimination of TB (less than 10 cases per one million inhabitants) by 2035 and TB elimination (less than one case per one million inhabitants) by 2050. Germany belongs to the addressed countries and territories with a TB incidence lower than 10 cases per 100 000 inhabitants. To reach these targets, Germany would have to have an annual reduction in the TB incidence of about 10% [1, 2].

However, electronic TB notification data available for 2001 through 2014 indicate an end of the declining trend for Germany (figure 1): case numbers and notification rates in the past 2 years exceeded the levels of 2012, reaching 4488 TB cases and 5.6 cases per 100 000 inhabitants in 2014 [3]. This observation is supported by more in-depth analyses.

First, we investigated the 5-year TB trend in terms of average percentage changes in case notification rates as suggested by the WHO [4] and the European Centre for Disease Prevention and Control (ECDC) [5]. We observed an average increase of 0.9% per year over the period from 2010 through 2014, while all previous 5-year spans showed decreases (figure 1).

Secondly, we assessed whether the 6.3% increase in TB notification rate for 2014 compared to 2012 was statistically significant using the z-test to compare two proportions (5% level of significance; two-sided).