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Editorial: **The treatment of multi-drug resistant tuberculosis – a return to the pre-antibiotic era?**

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*We as scientists have an obligation to address the ethics of transnational research, the distribution of drugs of the so-called 'diseases of poverty'… (*Beyers & Chan-Yeung 2003)

When the eyes don't see the heart doesn't feel (Spanish proverb)

When Magdalena was 15 years old she was diagnosed with smear-positive pulmonary tuberculosis (TB). She lived with her mother, a stepfather and 13 siblings in a very humble dwelling in an Andean country. Her stepfather would often beat her because she was unable to perform her assigned domestic chores. As a result, she would flee and abandon her treatment. She was prescribed several regimens which she took erratically. Three years later she was still smear-positive; the chest X-ray showed multiple cavities in both apices and drug susceptibility testing confirmed resistance to isoniacid (H), rifampicin (R), ethambutol (E) and streptomycin (S). The following year she became pregnant and died of respiratory insufficiency 6 months later.

Peter is a 45-year-old primary school teacher in an Eastern African country; he lives with his wife and several children. In September 2000, he was diagnosed with smear-positive TB and was given the category I regimen (2HRZE/6HE; Z = pyrazinamide); at the completion of treatment he was still smear-positive. Despite taking the category II regimen (2HRZES/1HRZE/5HRE) twice, he remained smear-positive. He saw a consultant in the capital who prescribed the entire gamut of second-line TB medications. The only drug which Peter was able to find was ciprofloxacin, which he took for several months. His latest drug susceptibility tests have demonstrated resistance to H, R, E, S and ciprofloxacin; the chest X-ray shows multiple cavities, especially in the left lung. He remains weak, emaciated, dyspnoeic and smear-positive.

These two patients from different continents had two characteristics in common: first, they suffered from a very serious form of TB; and secondly, they could not be treated adequately for lack of medication. Let us briefly examine the reasons underlying their clinical condition and lack of effective treatment.

Resistance to TB medications

All patients harbouring large numbers of bacilli have some mutant organisms resistant to one anti-TB drug. The number of these resistant bacilli is minimal compared with the population of susceptible bacilli and will be of little clinical significance as long as the patient is not exposed to an inadequate therapeutic regimen. Large numbers of resistant bacilli are the consequence of human intervention, which, by selecting the few naturally existing resistant bacilli, afford them a microbiological and clinical role they would not have under 'normal' conditions (no exposure to anti-TB drugs).

Resistance cropped up almost as soon as the modern era of TB treatment began, more than 50 years ago, when streptomycin was administered as monotherapy (Crofton & Mitchinson 1948). Many patients with meningitis were cured, but those with pulmonary TB and large bacillary populations rapidly became resistant. Because naturally mutant bacilli are resistant to only one drug (resistances to different drugs are not linked and are therefore highly unlikely) the detection of resistance to more than one anti-TB medication implies a multi-step selection process: the patient must have received a sequence of several non-curative regimens. The result is a sick person who, through faulty human intervention, has been transformed from a patient suffering from a fully drug-susceptible disease into a patient suffering from a multiple drug-resistant disease. Resistance to the two most effective drugs, isoniacid and rifampicin, is termed multidrug-resistance (MDR); its treatment is far from easy and frequently results in failure or even death (García-García *et al.* 2000; Lockman *et al.* 2001; Mukherjee *et al.* 2004).

MDR-TB in the world

Little attention was given to MDR-TB until the last decade, as it was not considered to be an important problem. A

group from Denver had given due attention to this issue (Iseman 1993) but it was not until several outbreaks took place in the United States (Dooley *et al.* 1992; Pearson *et al.* 1992; Frieden *et al.* 1993; Salomon *et al.* 1995) that the world began to take notice.

Two surveys by the WHO and the International Union against Tuberculosis and Lung Disease using standard guidelines revealed that resistance to TB medications was universal but varied greatly between countries and specific areas. MDR-TB was detected in several 'hot spots' but had a very uneven distribution in the world (Espinal *et al.* 2001). These surveys generated important data and demonstrated the urgent need to address this issue on a global scale and, more specifically, in areas with scarce resources. Globally, MDR-TB is not decreasing. In 2005, more than 1% of patients diagnosed with TB who had never received treatment were MDR (World Health Organization 2005).

Access to second-line anti-TB medications

Under the auspices of WHO, a Working Group on DOTS-Plus for MDR-TB was formed in 1999 with the main objective of preventing further spread of this man-made phenomenon. Securing second-line drugs at significantly reduced prices was one of the Group's major achievements. It was decided that second-line drugs should be made available only to specialized units linked to a laboratory capable of performing reliable drug susceptibility tests. At present, a project for treating patients with MDR-TB has to be submitted through a National Control TB Programme with its government's support and follow the guidelines developed for establishing DOTS (directly observed treatment short course)-Plus projects. Then, if approved by a Green Light Committee set up by WHO and comprising several institutions, cheap second-line drugs will be made available under strict supervision (Gupta *et al.* 2001, 2002).

Pending issues

Patients with MDR-TB, such as Magdalena or Peter, who live in a country where no DOTS-Plus projects have been approved, will be unable to obtain effective drugs. The resolution of their disease will depend entirely on its natural course. Faced with this situation, several controversial issues merit discussion.

Availability of cheap second-line drugs

Cheap second-line drugs are unavailable (unless through Green Light Committee-approved projects) because of the fear that their inadequate use will create further resistance. This argument is not fully justifiable as the only people who need second-line drugs are those patients who already have some degree of resistance; patients with fully susceptible bacilli receive the more effective first-line drugs. 'The possible loss of second-line anti-TB drugs due to resistance does not take us back to the 1940s' (Brown 2004): our patients *are already* in the pre-antibiotic era and will remain there until their demise! It is ironic that because of the concern of contributing to the difficulties in managing a serious clinical condition – which we may have created – we refuse curative medications to patients suffering from this condition. WHO has established that no intervention against MDR-TB should be undertaken unless it can be implemented countrywide (Espinal *et al.* 1999). This is tantamount to refusing treatment to all patients with TB (drug-resistant or not) in a particular country unless a well-functioning National TB Control Programme is in place.

Prevention is better than treatment

This argument, based on epidemiological and cost–benefit considerations, may be valid for those taking decisions away from the field. For a sick individual, discussions about prevention come too late and are irrelevant. Health personnel in close contact with patients find it hard to explain to them that their illness should have been prevented; that if they had not followed an inadequate regimen (because of poor adherence or because of faults in the health system) they would not harbour bacilli which we cannot eliminate with our available tools; and that the needed medications exist but that we cannot obtain them because of a poorly performing National TB Control Programme unable to deliver the much needed drugs correctly.

No DOTS-Plus until an effective DOTS Programme is in place

Several programme managers are of the opinion that no attention should be paid to patients suffering from MDR-TB as long as the number of successful treatments among susceptible patients does not reach a significant proportion. A patient who has failed with the first treatment (category I) and who may have resistant bacilli will be given the re-treatment regimen (category II) as a last chance and if no cure is achieved not much else will be offered. This regimen not only fails to cure MDR-TB but can further increase resistance (Espinal *et al.* 2000; Furin *et al.* 2000; Noeske & Nguenko 2002; Han *et al.* 2005), as only streptomycin is added to the original regimen. There have already been calls for its discontinuation (Espinal 2003). Although this reasoning may

seem logical (Why try to cure the 'difficult' patients while we are unable to cure the 'easy' ones?) I do not share this view: treatment of patients with TB under a National TB Control Programme is not a zero-sum equation. Adequate care of the small numbers of patients with MDR-TB does not necessarily have to impinge on the treatment of the large number of susceptible patients (Sterling *et al.* 2003). In fact, the technical and financial support required for treating patients with MDR-TB could strengthen the National TB Control Programme (Kim *et al.* 2003) and, eventually, the entire health system.

Transmission of MDR bacilli

An important issue that requires urgent action is the fact that patients with MDR-TB not receiving treatment are excreting highly dangerous bacilli until the day their disease spontaneously cures itself or until they die. It has been shown that MDR bacilli are effectively transmitted from person to person and may cause infection and disease (Kritski *et al.* 1996; Schaaf *et al.* 1999; Van Rie *et al.* 2000; Teixeira *et al.* 2001). The treatment of contacts of patients with MDR-TB poses several problems as studies demonstrating the effectiveness of any particular treatment are scarce and no consensus has been reached on the best prophylactic regimen (Fraser *et al.* 2006).

Do patients with MDR-TB have a right to be treated?

The world has not shied away from offering complex regimens with potentially toxic and expensive medications that must be administered for life to people with HIV. The '3 by 5' initiative of WHO and partners aimed to put on treatment no less than 3 000 000 persons (Mukherjee 2004). There is no reason why people with other infections should be denied rights that have been recognized for HIV patients. Why is it that what is a good for AIDS patients is not a good for others also? (Ollé-Goig 2004).

We urgently need to face the multiple issues related to MDR-TB. It is imperative to find a solution to the dilemma of universal access to second-line drugs in order to save the patients with this form of TB, which carries a very poor prognosis when not treated. Neglecting this problem will increase the disparities in the care of our patients, and our goal of greater equity will be pushed further out of reach.

Dedication

I dedicate this article to the patients with MDR-TB who I have cared for on the American and African continents who could not obtain adequate treatment.

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