

SHORT REPORT

Isolation unit for multidrug-resistant tuberculosis patients in a low endemic country, a step towards the World Health Organization End TB Strategy

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SUMMARY

Tuberculosis (TB) remains a threat to public health and is the second cause of death due to a single infectious agent after HIV/AIDS. The worldwide distribution of TB is heterogeneous. The incidence is decreasing in most high-income regions, but the situation remains worrying in many parts of the world. The emergence of *Mycobacterium tuberculosis* strains resistant to key agents used in treatment (rifampin and isoniazid) contributes to TB transmission around the world. To achieve TB elimination, both high and low endemic countries must upscale their efforts to decrease disease transmission and improve cure rates. Management of drug-resistant TB is of particular importance. In this paper, we discuss the different models of care of multidrug-resistant TB (MDR-TB), the ethical considerations and the specific constraints present in high income countries. The management model chosen by the Belgian TB specialists in accordance with public health authorities as well as building of a specific MDR/XDR-TB isolation unit are also discussed.

Key words: Antibiotic resistance, health policy, infectious disease control, public health emerging infections.

MAIN TEXT

According to the last World Health Organization (WHO) report, tuberculosis (TB) remains one of the world's largest infectious threats with an estimated 9·6 million new cases occurring in 2014, among which an estimated 480 000 cases are multidrug-resistant TB

(MDR-TB), i.e. strain resistant to rifampin and isoniazid [1]. The worldwide distribution of TB is heterogeneous. In the WHO European region, an estimated incidence of 340 000 cases has been reported in 2014, particularly in Eastern countries. The countries of the former USSR count the world's largest percentage of drug-resistant TB among their cases. This means that Europe remains far from TB elimination and is threatened by the Eastern MDR/XDR-TB (MDR-TB plus resistance to any fluoroquinolone and one of the injectable anti-TB drugs) outbreak.

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The current management of MDR-TB is characterized by long treatment duration, the high rate of side effects and a prolonged infectious period. Only 50% of MDR-TB patients in the WHO 2012 cohort of detected cases were successfully treated [1].

In Belgium, as in other Western European countries, TB epidemiology is characterized by a low rate of transmission in the general population but a high rate in some at-risk groups. In 2014, the incidence was 8.6 cases per 100 000 habitants with 959 notified cases, among them 2% were MDR-TB. Most MDR-TB and all XDR-TB occurred among asylum seekers, mainly from Eastern Europe. In addition, the resistance profile of the TB strains tends to worsen with time [2].

Currently, the Belgian model of care for TB profits from the close collaboration between two non-profit care associations in charge of lung health and TB (Fonds des Affections respiratoires (FARES)/Vlaamse Vereniging voor Respiratoire Gezondheidszorg en Tuberculosebestrijding (VRGT)) and the Belgian Lung and Tuberculosis Association (BELTA-Tbnet). The latter association is publicly funded and covers all out-of-pocket payments related to TB, with MDR-TB patients representing the largest part of the budget. Because MDR/XDR-TB cases are complex an MDR-TB expert committee was created in 2011. This multidisciplinary group, collaborating with the European Respiratory Society-WHO-e-Consilium proposes recommendations and advice to colleagues confronted with these complex MDR-TB cases. All these measures allow optimal treatment and careful use of new drugs to avoid the emergence of more resistant TB strains.

As of 1996 the Belgian national health system set up an 'Emergency medical care' programme. The patient receives appropriate care independently of his/her citizenship. Moreover, since 2005, access to TB diagnosis and treatment is free for all persons in Belgium. Asylum seekers from high endemic countries are screened for TB shortly after arrival. If MDR-TB is suspected, then patients are sent to the specialized TB centres where they receive up to date care. Such facilities are mainly available in university hospitals, situated in big cities. This can be very disruptive for the asylum seeker who is already dispersed in various regions across the country to avoid residential segregation and ethnic ghettos.

According to this practice, 178 MDR-TB cases have been treated in Belgium since 2005. Among them 20 were XDR-TB and 52 were pre-XDR (MDR-TB

plus resistance to any fluoroquinolone OR one of the injectable anti-TB drugs), 51.2% of cases originated from Eastern Europe [2]. The number of MDR-TB treated in our country has remained stable in recent years but the profile of resistance is showing a worsening trend. The most complex XDR-TB cases are preferentially referred to Saint-Pierre University Hospital (SPUH), which hosts the largest infectious unit dedicated to emerging infectious diseases in Belgium. In this setting, negative pressure rooms together with anterooms minimize the risks of transmission of airborne diseases to the health care workers and other patients. Following WHO guidelines for high-income countries, MDR-TB patients are strictly isolated in their rooms until they have three consecutive negative sputum cultures. The most severe cases remain hospitalized for months. After sputum culture conversion patients are discharged and ambulatory follow-up is assured by the FARES/VRGT teams. Physicians and specialized nurses perform medical follow-up, surveillance of treatment adherence and social support.

This highly specific management offers obvious advantages. First, it led to a huge TB treatment success rate of 86.8% in MDR-TB cases as well as in XDR-TB. Interestingly it is higher than the 77.7% success rate observed in susceptible TB cases that are easier to treat [2]. Second, this practice has enabled SPUH to acquire clinical experience and has increased our skills in the management of MDR-TB. In addition, this integrated strategy led us to assess experimental therapeutic scheme for difficult-to-treat XDR-TB cases by exploring, in particular, the effectiveness and safety of carbapenem-containing regimens [3]. The high rate of favourable outcomes in our cohort has contributed to the elaboration of new treatment protocols containing the association of meropenem with clavulanic acid for MDR-TB in Europe and Latin America. This led to a large retrospective cohort study confirming the encouraging results of the association meropenem with clavulanic acid added to an optimal background regimen when treating MDR- and XDR-TB [4]. More recently, the early bactericidal activity of meropenem plus clavulanic acid in human TB has been confirmed in a prospective study by Diacon *et al.* [5]. This drug association is now classified in the 2016 updated WHO guidelines in the group D 'Add-on agents'. Finally, this integrated management of MDR-TB and XDR-TB patients allowed us to control the spread of the infection in the community. Till now, no transmission in the

general population has been reported as confirmed by genotyping of all MDR-TB strains in the National Reference Laboratory of the Institute of Public Health. Currently, only two Belgian patients have contracted a pre-XDR-TB strain. One patient was infected in a primary care hospital by a patient whose TB diagnosis was made post-mortem. The second case occurred in a young woman working at the Immigration Office.

Conversely the hospital-based MDR-TB management presents some drawbacks. First, long stay in isolation rooms with minimal social contact and activity may cause patient distress and depression. Second, respiratory isolation imposed by the health care workers is sometimes difficult to accept and could lead to absconding, treatment withdrawal and even reluctances to look for care. Although the isolation of contagious patients could be made mandatory by law, it is difficult to put into practice. Staffs are not trained to deal with non-cooperative patients and wards are generally open places. Police officers are generally reluctant to assure such surveillance. This means that patients who do not adhere to treatment and infection control measures could lead to nosocomial TB outbreak. Finally, from an economic point of view, hospital care is expensive and long hospitalization periods in infectious disease unit decrease bed availability for acutely ill patients. The hospital administrators are more and more reluctant to provide such expensive management. Budgetary constraints could jeopardize this practice in the future.

All of these conditions led us to look at how we could impact on this constraining and expensive hospital-based management. The ambulatory approach, suggested by WHO, is an alternative. Many observational studies conducted in low- and middle-income countries suggest that ambulatory-based management of MDR-TB does not significantly worsen the percentage of favourable outcomes. In 2014, Weiss *et al.* published a meta-analysis of ten studies, including two studies performed in populations with a low percentage of XDR-TB patients [6]. They showed that 65% of 1288 patients reached a successful outcome, a rate comparable with previous series of patients treated in a hospital. The costs of ambulatory-based management of MDR-TB are much lower. Sinovic *et al.* showed that treating MDR-TB in the community could save 14%–32% of the budget assigned to MDR-TB management [7]. These observations combined with the lack of available hospital beds and the risk of nosocomial TB transmission in limited resource countries reinforce

the WHO recommendation for a decentralized ambulatory-based treatment of MDR-TB. However in these observational studies, the rates of TB transmission in the community are not evaluated.

The situation in a high-income country is different. Most TB cases are concentrated in big cities. In overcrowded urban environment, the first issue is optimal cure rate allowing a reduction of the transmission in the community. To achieve this goal, individually tailored treatments and close follow-up are the cornerstone of the TB management. This relies on the use of complex drug regimens, including daily intravenous injections (second-line injectable drugs, carbapenems), which are regularly reviewed and adapted. Because most MDR-TB cases treated in Belgium are asylum seekers and/or marginalized people, this complex schedule is difficult to implement in an ambulatory setting. At best, the patient lives in a centre for refugees where people live in very close quarters. At worst, he/she lives in the street where it is much more difficult to start and follow such a treatment. In our experience, homeless patients are more frequently lost to follow-up in the long term. Aside from the individual concerns, the possible mismanagement of these ambulatory contagious MDR-TB patients represents an increased risk of transmission within the community. Indeed TB outbreaks in shelters for homeless are well described. The next issue is the required period of isolation of patients with active TB. As early as 1976, Rouillon published a review based on epidemiological as well as experimental studies, suggesting that TB patients on effective therapy become non-infectious in <2 weeks [8]. This '2-week rule' is largely adopted in infection control guidelines. However, this statement is open to criticism because of the observational nature of most reports and the high prevalence of latent TB infections in the general population at the time of the studies. Moreover, most of these transmission studies were performed before the MDR-TB epidemic. In the case of MDR/XDR-TB cases, data about their infectiousness are scarce. In contrast with drug susceptible TB, establishing an effective treatment for MDR-TB requires complete and accurate results of drug susceptibility testing, which takes at least a 6–8 weeks. In terms of infection control, isolation until sputum culture conversion seems a more sound approach.

To preserve the advantages of centralized management while promoting humanization of the environment, SPUH aims to develop a specific isolation setting dedicated to MDR-TB patients. The main



Fig. 1. Two floors isolation unit blueprints.

objective is to encourage the patients to adhere to infection control measures by offering them a more human environment. Indeed involuntary isolation remains controversial [9]. In the case of *Enhorn vs. Sweden*, in which an HIV-positive man successfully challenged his detention by Swedish public health officials, the European Court of Human Rights has reaffirmed the lawful detention of contagious people but strict conditions must be respected: proportionate measure, absence of arbitrariness, dangerous disease

for public safety [10]. The priority objective of detention must be to care for the sick person and be used as a last resort and under human conditions. According to our opinion, isolation in a 12 m² room for months cannot be considered as 'human condition'. Therefore, the SPUH facility aims to decrease the feeling of detention by building a specific structure linked to the TB reference clinic, but separated from the main building. In this setting, patients would be allowed to go out of their room to exercise, for 'cigarette

breaks' or other social contacts. Considering that patients who are effectively treated are more likely to be less contagious, they could participate together in some entertainment activities, using a face mask if needed. Educational and psychosocial supports will be provided to improve treatment adherence and social integration after discharge. Patients will be treated in this unit until a safe ambulatory management can be organized. Some homeless patients will stay during the entire duration of the therapy to allow treatment success. In a worst-case scenario, this modern 'sanatorium' could be used for patients with the so-called 'totally resistant TB' with no treatment option in order to avoid further transmission within the community and provide palliative care. Linked to a university hospital, this 'difficult-to-treat' TB unit will also be a place for academic clinical management training and research to improve and maintain a high degree of skills in the treatment of TB in the medical community. From the economic point of view, the facility will relieve the acute units from those chronic patients who require reduced medical and nursing staff.

The ethical issues of this project were examined in 2012 by the Belgian Advisory Committee of Bioethics at the request of the Ministry of Public Health in the frame of the general policy against MDR-TB. At this time, the main concerns of the public health authorities were the lack of programmatic management and the fear of transmission within the general population. Because our project considered the social and economic needs of these patients, the infection control measures and the legal as well as ethical dimensions of mandatory detention, the Committee has supported our pilot-specific MDR-TB setting and the Ministry of Public Health endorsed its development. Construction started in 2016 on the roof of an existing building on the SPUH campus. All patient spaces will be provided with negative pressure with more than 12 air changes per hour, high-efficiency particulate air filtration and UV germinal irradiation to limit risk of disease transmission. It will be divided into two floors (Fig. 1). The first floor will include a negative pressure facility for patient hospitalization and a separate facility for health care workers. There will be ten rooms, including a larger one for mother and infant hospitalization. Patients will have access to the second floor by a specific lift. This relaxation area will have different spaces for a library, computer centre, physical and occupational activities and will give access to an outdoor terrace. A small kitchen and a laundry room will also be available.

Nursing care and medical supervision will be provided by specialized nurses and physicians.

In conclusion, the Belgian model of care for TB allows us to keep the burden of MDR/XDR-TB at a low and stable level. Despite a high percentage of successful outcomes and control of transmission to the community, this model based on the hospital-management of MDR/XDR-TB is expensive, very constraining and does not fit our definition of optimal medical care and humanity. With the building of a specific MDR/XDR-TB isolation unit closely linked to a reference university hospital, we hope to improve the quality of care and respect of TB patients' human rights while minimizing the risk for the community. This patient-centred approach, supported by public health ethics, is expected to open new perspectives in the medical care as well as emotional and social healing of patients suffering of MDR/XDR-TB.

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DECLARATION OF INTEREST

None.

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