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Tuberculosis, a re-emergent disease

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Abstract

Tuberculosis (TB) remains a major cause of morbidity and mortality worldwide. In Western Europe, regions with a high incidence of TB usually also have a high incidence of HIV infection; TB and HIV co-infection have increased over the past decade and among HIV infected patients, nearly half also develop TB. In settings where HIV is prevalent, TB drug resistance has also increased and several reports of TB and multi-drug resistant TB outbreaks, especially in health care settings, raise serious concerns about nosocomial transmission. Further research and new developments into more rapid diagnostic methods and sensitivity testing as well as the development of new anti-TB drugs are important to fight the disease. In addition, public health infrastructures have to be strengthened in order to increase adherence to TB treatment, where directly observed treatment strategy is the cornerstone for a successful outcome.

Keywords: Tuberculosis; *Mycobacterium tuberculosis*; HIV; Multi-drug resistance; DOTS

1. Increasing burden of tuberculosis

Tuberculosis (TB) is one of the oldest diseases known to mankind, and still remains the leading single infectious cause of death among adults [1]. All this happens although prevention, diagnosis and inexpensive and effective treatment are available.

One in every three people in the world is believed to be infected with *Mycobacterium tuberculosis*, and at risk of developing the disease. More than eight million new cases of TB develop every year and three million people die from the disease [2]. The number of deaths surpasses the number of those caused by heart disease, cancer or any other caused by an infectious agent [3]. Moreover, more than 90% of all TB cases and deaths occur in developing countries [4,5], where TB is already responsible for 20% of all deaths in adults. Countries with a high prevalence of HIV, particularly those in sub-Saharan Africa, have witnessed a great increase in the number of TB cases, with reported incidence rates increasing two- or three-fold in the 1990s [6].

All this illustrates the tremendous burden that a single disease has globally. This alarming situation prompted the World Health Organisation, in 1983, to encourage research into TB, and 10 years later to declare TB as a global emergency [7].

The discovery of anti-TB drugs in the 1940s, led to the belief that the prevalence of TB would rapidly decrease. As a consequence, the world became complacent to the TB problem; public health measures and research into the disease were almost abandoned. In the early 1990s, incidence rates stopped declining or even began to increase in the USA and in Western European countries [8].

Factors that are related to the high TB burden include the human immunodeficiency virus (HIV) pandemic, homelessness and poverty, as well as the widening gap between rich and poor, the increasing number of refugees, the reduction of governmental support in prevention and treatment programs [9].

2. TB and HIV infection

HIV infection has contributed significantly to an increase in the worldwide incidence of TB, and it is the single most important risk factor for TB. It is estimated that most people

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infected with HIV (90%) are in developing countries. Thus, in sub-Saharan Africa the association of HIV with TB is a great problem, and in some areas 70% of new TB patients are HIV co-infected [10,11]. Worldwide, TB is the most common cause of death among AIDS patients, killing one of every three of them.

Co-infection with HIV significantly increases the risk of developing TB [12]. Moreover, worldwide, most HIV infected individuals are also infected with *M. tuberculosis* [13]. A further increase in TB rates can be expected in areas with a high prevalence of HIV infection, considering that:

(a) As the rate of progressing from latent to active disease in these individuals is several times higher than in those without HIV infection [13].
(b) The reactivation rate is also much higher in HIV infected individuals (10% a year) when compared to 10% during life in non-HIV infected people [14].
(c) HIV infected individuals also have a faster progression from infection with *M. tuberculosis* to TB [15].

This has been seen in Africa and will become increasingly evident in Asia, where around 20% of all HIV-infected individuals live today.

HIV infected patients also have more frequently resistant mycobacterial strains. Several studies have shown an increased risk of primary and secondary TB resistance in settings were HIV is prevalent, and multiple reports of outbreaks of TB and MDR-TB have highlighted the speed with which HIV infected patients progress to active TB after infection with *M. tuberculosis* [16–18].

While some studies emphasized the impact of HIV on the natural progression of TB, other studies have demonstrated that TB may alter the natural history of HIV disease [19]. Viral load has been shown to increase during the course of TB and decrease with appropriate therapy. In addition, HIV patients with TB have a shorter survival and develop AIDS faster than those without TB. These findings emphasize the importance for an early diagnosis and effective treatment of TB, as well as prevention and control strategies for TB.

3. Multi-drug resistant tuberculosis

The already large problem of TB is further complicated by the emergency of *M. tuberculosis* multi-drug resistant (MDR) strains, presently estimated to affect 50 million patients. MDR-TB is a major public health problem and emphasizes the need for better TB control programs worldwide [20]. In some countries, MDR-TB prevalence can reach 50%, which underscores the importance of a well functioning directly observed treatment short course (DOTS)-program to reduce TB and MDR-TB prevalence rates [21].

Treatment for MDR-TB is more costly and problematic, less effective and more prolonged (18–24 months) than the fully sensitive TB. Overall mortality rates with these strains are 40–60% in non-HIV infected individuals and are even higher in HIV-infected patients (80%) [22].

4. TB control using the DOTS

The lack of adequate public health infrastructure has also been shown to contribute to the resurgence of TB as was demonstrated by several recent outbreaks [17,18,23–31]. TB control relies on prompt diagnosis and effective treatment, which allows interruption of the chain of transmission. In this way, the WHO has promoted the DOTS strategy since the 1990s. The best intervention against the transmission of TB is the cure of all infectious cases.

5. Immunization

BCG vaccine, usually given at birth in most countries, has an overall efficacy that ranges from a negative value to 80% for preventing TB [32]. This highly variable efficacy of BCG can be explained with several factors, such as the presence of environmental mycobacteria, genetic factors and also the type of BCG strain used. Studies have shown that protective immunity correlates with the strains of BCG used, i.e. Glaxo versus Japanese BCG. Despite the observed controversial efficacy of BCG vaccination, it has been found to prevent the severe paediatric manifestations such as TB meningitis, which makes it a useful preventive intervention.

Individuals who are found to have a positive Mantoux test should be evaluated in order to rule out the possibility of active disease. However, in most countries the role of the Mantoux test for the diagnosis of TB is controversial as a positive result can indicate either active disease, infection in the past, or BCG vaccination.

6. Prophylaxis

According to the CDC guidelines, individuals that do not have active disease, are under the age of 35, and have a positive Mantoux test, should be started on isoniazid for 6–9 months (or rifampicin and pyrazinamide), in order to reduce the risk of active disease. This applies to both, HIV and non-HIV infected. These measures are justified as an attempt to reduce TB incidence and, in HIV infected individuals also to decrease the progression of HIV infection. However, data that supports these recommendations is based in only a few randomised studies [33–37]. Further complicating these arguments and in addition to the difficulties in interpreting the Mantoux test, another obstacle to this use of prophylaxis and implementing this as a strategy are the lack of specific diagnostic tests to exclude active disease. Moreover, there is a concern about the wide use of prophylaxis and the real possibility of creating drug resistance. New skin tests are needed, and results from studies using other proteins such as ESAT-6 and MPB-64, are expected soon [38,39].