



EDITORIAL

Tuberculosis: an ancient and evergreen disease

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Tuberculosis (TB) is a fascinating disease, and still represents a “special laboratory” for immunologists, pathologists, radiologists, respiratory physicians, paediatricians, public-health experts and other specialists. TB, after affecting mammoths and Egyptian mummies, has infected a large fraction of mankind (about one third of them, according to Mantoux-based estimates) of whom no more than 10% of the immunocompetent and up to 50% of immunocompromised individuals, at the end, develop the disease [1, 2].

Due to the consistent transmission rules of TB and its role in medical history, TB epidemiologists have been forced to develop sophisticated epidemiological models aimed at better understanding TB and how better the disease can be controlled and, eventually, eliminated [3, 4].

According to the natural history model, one case of infectious TB is likely to infect approximately 10 persons per year for 2 yrs, thus generating 20 infected individuals [1]. Given that the lifetime breakdown rate (e.g. the proportion of individuals who will develop TB disease) is estimated to be 10%, and that ~50% of cases are likely to become sputum smear-positive, one infectious source is likely to add at least another infectious (sputum smear-positive) case to the existing community burden [1, 2]. The World Health Organization (WHO)-recommended interventions, from which the DOTS strategy expanded into the larger vision of the Stop TB Strategy [5], have been effective in decreasing the epidemic curve by recommending, in essence, a set of interventions which need to be implemented in order to reach the World Health Assembly targets, e.g. to ensure rapid diagnosis of 70% of existing sputum smear-positive cases and effective treatment of 85% of these cases. These interventions, representing the “juice” of TB control, have the potential to dramatically reduce the transmission of *Mycobacterium tuberculosis* within the community, e.g. by up to 40%. This would allow, in the absence of opposing external factors (e.g. increasing the breakdown rate, as well as known factors like malnutrition, diabetes, stress or immunosuppression [6]), a plateau of the epidemic curve in a given setting after 5–7 yrs following implementation of the control intervention.

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This has been demonstrated in countries such as Cuba and Peru, and recently in Europe [1, 7]. In Romania targets of 70–85% were achieved and, after an initial increase, both case load and case-fatality load were reduced [7].

Much has happened since the first sanatorium was opened in Germany in 1857 and since Robert Koch discovered, in 1882, that *M. tuberculosis* was the causative agent of TB [1, 8]. In 1897, the dispensary system was introduced in Scotland (UK). In 1907, C. Forlanini demonstrated that artificial pneumothorax further increased the chances of a cure by creating a difficult environment for the (aerobe) bacilli and, in the same year, streptomycin was introduced as treatment for TB, thus initiating the drug era. It also seems that a great deal of time has passed since the 1960s, when the last true first-line anti-TB drug (rifampicin) was introduced.

Other milestones of TB control including the bacilli Calmette–Guérin vaccination, Mantoux testing and chest radiography are also very old [1].

The article by CONNELL *et al.* [9] in the present issue of the *European Respiratory Review* provides a comprehensive overview of the recent discoveries and is a refreshing breath of novelty in the TB community. The article also provides an update on the main priorities the TB control community is facing, such as migration, TB/HIV and multi-drug resistance (MDR)-TB [9], as well as the environmental factors affecting the risk of acquiring TB disease given infection and the controversial issue of vitamin D deficiency and TB.

The most detailed section of the article focuses on new diagnostics for latent TB infection and disease, including interferon- γ release assays, nucleic acid amplification tests (Hain test and GeneXpert amongst others), other immunodiagnostic approaches, microscopic-observation drug susceptibility and lipoarabinomannan. Finally, the authors discuss new drugs and the role of corticosteroids in the treatment of TB [9].

The article by CONNELL *et al.* [9], as do several other available articles, correctly advocates for more research. If we look at the three classic areas, diagnostics, drugs and vaccines, there is no doubt that less was achieved in the latter two areas when compared with the first. We strongly agree that more research is necessary. In fact, the need for more research has become the sixth element of the WHO-recommended strategy of TB control, the Stop TB Strategy [5].

A question is likely to be immediately generated in a non-TB specialist's mind when reading a similar review: why, if we have all the necessary ingredients (new diagnostics, effective drugs, with some news on the horizon, and a vaccine, with

promising better ones in the pipeline, and even a strategy), has TB not been eliminated yet?

The question appears simple to answer, but it is not. The reasons why our generation of TB controllers will be able to retire without any risk of becoming redundant are many, and their interactions multifactorial.

We need to go back to the time (1990, Wolfheze, the Netherlands [10]) when Europe committed itself to reach elimination (the point at which less than one infectious (sputum smear-positive) case per 1,000,000 inhabitants emerged annually in the general population), e.g. a condition in which existing sources of infection (sputum smear-positive cases) are too jeopardised to allow a consistent fuelling of the tank of infected individuals from which future cases of TB are likely to occur. An integral part of the strategy is the systematic, aggressive search of newly infected individuals [11] who will undergo treatment for latent infection with a substantial, progressive reduction of the pool of infected cases and, consequently, a reduction in the number of future cases.

The modern strategy to control and eliminate TB in the low-incidence European setting is presently based on risk-group management and outbreak management [4]. Despite the gradual decrease in TB incidence in the general population, TB is still prevalent in definite risk groups requiring a specific intervention strategy. Furthermore, outbreaks are also becoming common, requiring contact tracing in concentric circles (the stone-in-the-pond principle) [11] and treatment for infected individuals to prevent future cases of infectious TB from occurring.

What is happening at the global level and in Europe? K. Styblo, the father of modern TB epidemiology, predicted with a certain precision the beginning of the elimination phase [1]. His calculations, performed before computers appeared, were based on the historical reduction of age-specific TB incidence rates among military recruits in the Netherlands. His model generated hopes and (epidemiological) ambitions [12].

Unfortunately, several factors disturbed the dynamic preventing this scenario from materialising as previously estimated: 1) the HIV co-infection, particularly in Sub-Saharan Africa, fuelled TB in an unprecedented manner; 2) the migration flow prevented even the best programmes from reaching the elimination phase, through a continuous settlement of infected individuals from high TB-burden countries; and 3) the emergence of MDR-TB, and then of extensively drug-resistant-TB [13, 14], brought us back to the pre-antibiotic era [15]. Although, in absolute numbers, the contribution of these cases in Western Europe is low (being much higher in the former Soviet Union countries), they pose pressure on national TB programmes.

The management of MDR-TB cases is very expensive (up to €100,000 just to purchase drugs for the most severe cases) and requires long periods of hospitalisation, adequate laboratory and infection control practices [16], and qualified centres to manage them [4].

The new discoveries described in the present issue of the *European Respiratory Review* [9] will be extremely useful to improve TB control over the next 10 yrs, with the hope that Europe will be able to enter the elimination phase.

To allow this step forward, we need to be supported by a strong public-health effort aimed at providing universal access to quality anti-TB and anti-HIV drugs, in the context of a strong TB control programme engaging all healthcare providers having the patient at the centre of the system [17].

STATEMENT OF INTEREST

None declared.

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