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Foreword

A concise guide to TB control

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“...The fight against tuberculosis should be included in the Flagship Europe 2020 Strategy...” (Declaration by the European Parliament, 3 February, 2011) [1].

Several excellent textbooks on TB exist, such as *Tuberculosis and the Tubercle Bacillus* and the three-volume set of the *Handbook of Tuberculosis*, to name a few [2–5]. So why this new e-book on TB? This book focuses on the salient issues of TB control by medical measures: diagnostics, therapeutics and vaccines. Although TB has troubled humankind for millennia, and had its height in 19th Century Europe, it has not come under our control until today. In the first decade of the 21st Century, up to 100 million individuals developed active TB and up to 20 million sufferers died – more than in any previous decade. More than 2 billion individuals are latently infected with the etiologic agent *Mycobacterium tuberculosis*, but they have succeeded in keeping the pathogen in check. These people, a third of the world population, however, remain at risk of developing TB during their lifetime since the pathogen is not eliminated but persists in a dormant stage with low metabolic and replicative activity. As a consequence of immune debility, *M. tuberculosis* becomes metabolically active and causes TB disease in 10% of all latently infected individuals at some point in their lifetime.

In the beginning of the last quarter of the 20th Century, there was a glimmer of hope that TB could be brought under control; however, this was dashed

with the emergence of HIV/AIDS. HIV compromises the immune system, which needs to be competent for control of latent *M. tuberculosis* infection, and hence increases risk of active TB manifold, from 10% risk over a lifetime to 10% risk within the year of coinfection.

We know how to diagnose TB accurately, yet, in developing countries where TB rampages most, TB diagnosis still depends on the microscopic detection of acid-fast bacilli in sputum smears. This test was described in principle by the discoverer of TB, Robert Koch, in 1882 and is coming of age. In fact, almost half of all diagnosed TB patients are smear-negative, that is, false negative for TB by this method. It is, therefore, rewarding to witness an active pipeline of new diagnostic tests. The most advanced test in the field, the GeneXpert®, not only detects the etiologic agent of TB, *M. tuberculosis*, but also determines its resistance against rifampin as marker for multidrug-resistant TB.

We have multiple drugs to cure TB. However, with the emergence of multi-drug-resistant TB and extensively drug-resistant TB, resistant against the two major first-line drugs, or against virtually all first- and second-line drugs, respectively, our armamentarium has become scanty. Consequently, many TB patients have no access to adequate treatment. Knowing that TB drug research and development was at its height between the early 1950s to late 1960s and then followed by a phase of quiescence until the beginning of this century, this is not surprising. Drug treatment of TB is complicated and protracted, necessitating at least three different drugs administered for 6–9 months, rendering patient compliance far from perfect. This situation serves as a most fertile ground for the emergence of drug-resistant strains.

We have a vaccine against TB which was developed between 1910 and 1920. This vaccine, bacillus Calmette–Guérin, indeed protects newborns against severe forms of TB but is unable to protect against pulmonary TB in adults.

Obviously, new TB drugs, diagnostics and vaccines are needed if we want to bring the threat of TB to an end in the 21st Century.

- These drugs should be active against drug-resistant TB of different degree;
- They should not antagonize antiretroviral therapy against HIV, for treatment of patients suffering from both diseases HIV/AIDS and TB;
- They should act on dormant *M. tuberculosis*, which not only exist in latent infection but also coexist with metabolically active *M. tuberculosis* in active TB disease.

New diagnostics are needed that allow us to:

- Diagnose all TB patients, including sputum-negative sufferers of extrapulmonary TB;
- Distinguish between latent infection and active TB;
- Predict the risk of TB reactivation in *M. tuberculosis* latently infected healthy individuals.

New vaccines are needed that are better than BCG:

- These vaccines must protect not only toddlers but also adults;
- They should be effective when administered preexposure and postexposure with *M. tuberculosis*;
- Ultimately, next-generation candidates should be capable of eradicating or preventing infection with *M. tuberculosis*, while current vaccine candidates are aimed at preventing active TB disease by controlling latent *M. tuberculosis* infection.

Research and development for intervention measures in TB have made significant progress. A search for publications in PubMed on TB revealed that the number of papers published in the last decade of the 20th Century was half the number of papers in the first decade of the 21st Century. Notably, clinical studies on TB showed a steep rise by 2.5-fold. This can be directly linked with an increase in annual funding for TB research and development from less than US\$100 million at the turn of this century to more than US\$500 million in 2010. While this increase is highly laudable, further financial commitments are called for [6,7]. In the long term, these investments will pay back by reducing the huge cost of TB patient care. Current expenses for TB cure, including cost for drugs, medical care and loss of workforce, have been estimated to be at least US\$20 billion annually. A tenth of this (US\$2 billion) per year over the next 10–20 years is needed to push and pull candidates for new diagnostics, drugs and vaccines through their clinical trial pipelines. Only with the help of new intervention measures can the ambitious goal to eliminate TB by the year 2050 be approached, which was proclaimed by the Stop TB Partnership with endorsement by the WHO [8]. Note that elimination of TB is defined as one new TB case in 1 million population.

This eBook comprises five chapters each written by experts in their respective fields. Chapter 1 by Huq and Davies describes the dire, current global situation of TB and emphasizes the need for TB intervention measures over the next decade. Chapter 2 by Pai *et al.* focuses on new developments in

TB diagnosis. Chapter 3 by Migliori *et al.* provides an overview of currently used drug regimens and global guidelines for their use. This is followed by Chapter 4 by Upton and Ma, describing new TB therapeutics in the research and development pipeline. Last but not least, Chapter 5 by McShane and Rowland provides an overview of the pipeline of the first generation of new TB vaccines.

I hope that by concentrating on the salient features of new and current intervention measures against TB, this book can fill a gap for the reader interested in a concise update on TB control by medical means.

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