Tuberculosis in the Twenty-First Century

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With an estimated two billion people being carriers of latent tuberculosis infection (LTBI), the gains achieved by increasing access to diagnostics and treatment, although substantial, have had a modest impact on the global burden of tuberculosis (TB). At the same time, increased access to treatment has had the unintended consequence that drug-resistant TB (DR-TB) has increased dramatically. Earlier TB control strategies strongly emphasizing medical treatment have failed to address these issues effectively.

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1. Introduction

Broadly accepted estimates inform us that at least two billion people—25–30 percent of the world's population—are carriers of latent tuberculosis infection (LTBI) [1]. According to WHO estimates, 10.6 million new cases of active tuberculosis (TB) infection developed in 2021 [2], which was a slight decrease from 11.2 million reported in 2000, as an estimated decline in incidence rate from 184 to 134 since the late 1990s was almost canceled out by the global increase in the human population. Furthermore, the syndemic synergies[3][4] between the COVID-19 pandemic and TB led to an increase in estimated TB incidence in 2020–21 [2].

The modest progress in TB control should be assessed against substantial increases in funding for the global TB control program since 2000 and, in 2015, the introduction of a strategy to eliminate TB and the launch of a new 'paradigm' to achieve this end by 2030.

2. Latent TB Infection

LTBI is unevenly distributed globally, which is more likely to be around forty percent in high-burden countries. Active TB disease manifests in five to ten percent of all LTBI cases and can, in theory, happen to any infected person but is usually facilitated by prior weakening of the immune system and follows the fault lines of exposure and late diagnosis that go together with poverty, high population density in poor neighborhoods and poor nutritional status.

Development of clinically manifest TB disease among LTBI carriers has some degree of predictability among so-called risk groups, such as those co-infected with HIV or living in close contact with TB patients. A treatment guideline for preventive treatment released by the World Health Organization (WHO) in 2020 [5] recommended medical treatment for LTBI in such cases. However, the guideline also acknowledges that 'other people at risk'

such as dialysis and silicosis patients, in addition to socially defined populations such as migrants from countries with a high TB burden, homeless people, prisoners, health workers, and people using drugs, may be screened and given preventive treatment (conditional recommendation) even if the effect is uncertain. In addition, children and adolescents with LTBI have a higher risk than adults for developing TB disease and have recently been recommended for preventive treatment [6]. Whereas the underlying paradigm thus recognizes the importance of living conditions among people with LTBI, the solution remains one of (preventive) medical treatment without addressing the conditions causing their increased risk of active infection.

3. Increase of Drug-Resistant TB Incidence

The overwhelming presence of LTBI is one of several reasons why the so-called DOTS (Directly Observed Treatment—Short-course) strategy promoted by WHO since the mid-1990s has had limited success in addressing TB as a global health problem even if the strategy increased access to effective treatment for millions of patients. Another reason is its inability to effectively manage the growth of drug resistance that the strategy was supposed to prevent. Whereas the overall trend for the global incidence of TB has been slowly declining, and a similar trend for drug-resistant TB (DR-TB) in Europe has affected the global trend positively [2], in most high-prevalence countries, DR-TB has increased. However, despite improvements in the global surveillance of DR-TB [7], the quality of statistics is subject to several biases. Notably, it depends on case detection, with large groups of patients never being diagnosed. To add to this problem, there is a growing concern that drug resistance is also slowly increasing among the world's LTBI cases [5], threatening to undermine current LTBI regimens in the future. As DR-TB is a direct consequence of medical treatment, a brief introduction to the recent history of global health efforts to control TB through treatment-based interventions is provided below.

4. Directly Observed Treatment—Short-Course (DOTS)

Until the 1990s, TB was, in many countries, a neglected disease. In the rich countries, it had disappeared as a public health priority, hidden from political attention in marginalized populations such as the homeless, migrant workers, and poor neighborhoods with little access to healthcare services. In low-income countries, funding for healthcare and other essential deliverables of the state had been severely reduced due to so-called restructuring programs imposed by global financial institutions, often in collaboration with dysfunctional forms of governance characteristic of postcolonial power structures. Unlike other conditions in this category, such as malaria and other vector-borne diseases that were considered 'tropical' for ecological reasons, TB was pushed into the category of 'tropical diseases' due to its relative disappearance from high-income countries. However, due to its syndemic dynamics with human immunodeficiency virus (HIV), it reappeared on the radar of the global north, and in 1993, WHO declared TB a global public health emergency [8]. This call for attention followed the introduction in 1991 of the so-called DOTS strategy, which was in need of substantial funding for global implementation.

DOTS is an acronym for Directly Observed Treatment, Short-course, 'short' referring to six months. It was a highly complex health intervention [9] that required simultaneous interventions at many health system levels and

depended on the quality of the existing health infrastructures despite its vertical design. ‘Directly observed’ meant that the patient was in contact with a so-called DOT-provider (DP), and they then had to visit the DP and take medicine in front of this person. The DOTS approach was developed in response to problems with patient adherence to earlier unsupervised treatment regimens of even longer duration. As has been pointed out by Ogden and others, DOTS could be criticized for moving away from ‘models of communication and co-operation between providers and patients’, ‘back to a traditional medical approach with the patient as the passive recipient of advice and treatment’ [10], representing a paternalistic and context-free response to the challenge of premature interruption of treatment [11].

In addition to directly observed treatment (DOT), the concurrent need for access to diagnosis through sputum microscopy, uninterrupted availability of high-quality drugs for the entire treatment period of each patient, and a comprehensive monitoring system resulted in a highly complex health intervention that required considerable political backing at all levels. In a high-burden country such as India [12], the backdrop against which DOTS was implemented was a poorly functioning TB control program that, according to an evaluation, ‘suffered from managerial weaknesses, inadequate funding, an over-reliance on x-ray for diagnosis, had frequently interrupted supplies of drugs, and low rates of treatment completion’ [13] (19). There was an urgent need for policy change, and WHO advocated DOTS as an answer to the problem.

The increased access to treatment was celebrated as a success. DOTS was based on a calculation that with a case detection rate of 70% of all actual cases and a cure rate of 85%, the TB caseload could be cut by half within a decade [14], using combination therapy with four different types of antibiotics, which were given during an ‘intensive phase’ of two months followed by a ‘continuation phase’ of additional four months. Also, being a multi-drug regimen, it was intended to control the risk of developing drug resistance. Whereas DOTS represented an improvement in TB treatment relative to the earlier neglect situation, it soon became evident that increased access came with the cost of growing drug resistance. In contrast, the hoped-for decline in the incidence rate was barely visible. Patients with relapse after treatment or where treatment had been interrupted for at least two months were routinely placed on a different regimen including injectable Streptomycin, but as pointed out elsewhere [15], access to drug susceptibility testing during the 1990s and 2000s had been minimal.

India is a high-prevalence country with a significant disease burden attributable to TB, accounting for around 25% of TB cases worldwide. In India, DOTS was launched in 1993 and was gradually scaled up from an initial coverage of 2.35 million people to nationwide coverage by 2006. Towards the end of the 2000s, the upgrading of laboratories and availability of medicines for patients who tested positive for drug resistance began to slowly change the Indian treatment scenario. This also led to dramatic changes in the figures involved: an estimate of 99,000 new multidrug-resistant TB (MDR-TB) cases annually by 2011 was quoted by a leading national expert [16], whereas only 4217 patients had been placed on relevant treatment by the end of 2009, of whom only 756 were alive 12 months later.

5. Revising the TB Control Strategies

The problem of the rising number of DR-TB cases and the need for urgent action had been pointed out as early as the late 1990s. Farmer and colleagues [17][18] argued in favor of individualized treatment regimens for MDR-TB. Realizing the alarming situation but insisting on standardized treatment for resource-poor settings, WHO developed guidelines for the so-called DOTS+ strategy [19] as a first step towards programmatic treatment of DR-TB, launched as the 'STOP TB' strategy that would cover the period 2006–2015. In addition to standardized treatment for DR-TB, the strategy would strengthen collaboration with HIV services and develop new diagnostics "supported by a budgeted plan with feasible targets" [20]. DOTS was still considered a success in terms of increased access to TB treatment in lower-income countries, even if the somewhat optimistic prediction regarding its ability to reduce TB prevalence and prevent drug resistance was proven wrong. Nevertheless, STOP TB was launched with similar optimism. With the Stop-TB strategy, "by 2015, global TB incidence could be reversed and its prevalence and mortality reduced by half compared to 1990" [20].

Realizing the limitations of DOTS and the growing problem of DR-TB, WHO and other global health actors engaged in TB control have regularly modified the TB control strategies during the past twenty years, eventually launching the 'End TB Strategy' in 2014 [21]. At the same time, the UN-hosted Stop-TB partnership called for a paradigm shift away from a near-exclusive focus on medical treatment and towards so-called patient-centered and community-oriented approaches to TB control. A central document describes this paradigm shift in predominantly 'social' (as different from 'medical') terms, e.g., 'Medical interventions alone will not be enough to end TB. Nonmedical actions and investments, such as improved housing and sanitation, poverty reduction, and strengthened social safety nets will drive down the number of people becoming ill and dying from TB' [22]. At the same time, the new strategy calls for integrated health systems, including integrating TB interventions with HIV/AIDS and maternal and child health programs. These reorientations can perhaps be seen as an attempt to consider the syndemic potentials and well-established synergies with other epidemics and socioeconomic and other inequalities in global TB control, even if the concept of syndemic is absent from the strategic documents.

A paradigm shift in the context of scientific knowledge according to Kuhn [23] follows a period of crisis in which old assumptions and methods are challenged and need to be replaced by new ones. The brief history of TB control since the 1990s provided above points to such a crisis. however, what is labeled as a paradigm shift by WHO builds on existing TB control strategies with medical treatment at the center while new priorities and methods are added. An actual paradigm shift may require the development of a biosocial [24] understanding of the entanglements of pathogens such as TB and the lives and life circumstances [25] of their hosts to reconfigure prevention approaches in a world where LTBI is part of the human condition.

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