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Mini Review

Tuberculosis: renewed challenge in Brazil

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Abstract

This article reviews tuberculosis control actions performed over the last decade, at a global level. The perspectives for the fulfillment of the goals of the new Global Tuberculosis Elimination Plan are described, where the insertion of social protection (Pillar 2) and research (Pillar 3) will play an innovative and strategic role, especially in high-burden countries, like Brazil.

Keywords: Research. Tuberculosis. Strategy. Diagnosis. Prevention. Treatment.

For millennia, tuberculosis (TB) remains a public health problem[1-3]. Between 2000 and 2015, at the global level, 49 million patients survived through strategies that sought greater performance in TB diagnosis and treatment in high-burden countries. Despite this, TB has recently become one of the 10 leading causes of death worldwide and the highest cause of mortality among infectious diseases[3]. About 10.4 million people had TB and 1.8 million died (including 0.4 million among people with HIV). The World Health Organization (WHO) estimates that 480,000 subjects had multidrug-resistant tuberculosis (MDR-TB) and 10% of them developed extensively drug-resistant TB (XDR). Only 27% of MDR/XDR TB patients were adequately diagnosed and treated according to the drug resistance profile. In 2015, the WHO reported that the cure rate in TB, MDR-TB, and XDR-TB cases were 83%, 52%, and 28%, respectively[3].

In 2006, the STOP TB/WHO Global Plan focused on strengthening the health system (decentralization of TB control actions to primary care) and on adopting direct observed therapy strategy (DOTS) pursuing an increased treatment effectiveness in children with TB, TB/HIV, and MDR/XDR[4]. In the following years, TB treatment success increased (above 80%) in countries with high coverage of DOTS. However, at the global level, the annual decline in TB incidence remained low (1.5%) and insufficient to eradicate TB. In Brazil, the annual decrease of TB incidence did not exceed 2%, when the target reduction percentage would be approximately 8%, and the treatment indicators did not reach 75%, with regional differences[5].

Globally, in spite of the implementation of these strategies, the access and detection of TB cases remain unchanged, mainly among those living in large urban areas, with drug resistance, vulnerable populations (HIV-infected individuals, inmates, drug users, homeless, children, and adolescents) or with comorbidities [human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), mental health disorders, diabetes mellitus, and smoking][6-9].

WHO recognized that TB control actions should be conducted at different levels of health care (primary, secondary, and tertiary), including prisons. Recently, clinical and operational research have indicated that the approaches are more effective when they respond to local socio-cultural characteristics, organization of health service delivery, and type of community activities. These approaches should cover the

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cascade of actions that include local TB transmission control, screening, and diagnostic investigation of active and latent TB, followed by its antimicrobial treatment, incorporating biomedical approaches[9-13], biopsychosocial[8,14], strengthening social protection[15,16], community participation[17], and political commitment[18].

However, in high TB burden countries, operational research performed to cover such approaches are limited. Thus, the most appropriate interventions to control the epidemic at different healthcare levels cannot be identified[19,20]. This scenario may be result from the fragile interaction between researchers and TB and HIV managers, who prioritize activities in TB, TB/HIV care, or surveillance activities, but not research. In addition, favorable results obtained through research carried out in high burden countries, such as Brazil, usually do not have long-term sustainability and are not incorporated into the routine of the health system[21-24].

Among the most widely used interventions recommended by the WHO, we cite the adoption of an early diagnosis of drug-resistant and drug-sensitive TB using new technologies (usually molecular tests) aiming to adopt appropriate treatment and taking measures to control TB infection in the community[25-26]. Among the recommended molecular tests, the Xpert MTB/RIF test has already been adopted in 15 countries[3]. However, Creswell et al. and Albert el al. analyzing the use of Xpert MTB/RIF worldwide in the routine of Tuberculosis Control Programs reported difficulties in incorporating this molecular technique in different countries and provided limited impact on epidemiological indicators of TB, especially those related to treatment outcomes and/or interruption of TB transmission[27,28]. In addition, even with subsidies, in countries with high TB burden such as South Africa, the sustainability of its use under programmatic conditions has been questioned[29].

The use of Xpert MTB RIF in TB diagnosis was evaluated in five pragmatic clinical trials: studies of high scientific evidence and strength of recommendation, under routine conditions. When compared with smear microscopy, Xpert MTB increased the number of patients with bacteriologically confirmed TB and reduced the time between screening and initiation of TB treatment, but did not reduce mortality or lost to follow-up[30-34]. The impact of Xpert MTB/Rif on the occurrence of relapse or TB transmission in the community was not described.

Recently, incorporation of new screening, diagnostic, therapeutic, or management technologies has been highly recommended to routinely evaluate their impact (through pragmatic clinical trials) on the clinical and epidemiological indicators coupled with the bio-psycho-social aspects to the care process adopted in the local health system. Then, the use of new technologies may be incorporated to the National or Regional Clinical Guidelines[12-14,19,35-37].

In recognition to these challenges, the World Health Assembly in May 2014 approved the new Global TB Elimination Strategy with a set of ambitious targets, later included in the Sustainable Development Objectives 2030[38]. The new global strategy aims at reducing mortality and incidence of TB in all countries, targeting the indicators currently observed in high-income countries. This new strategy is based on three pillars: 1) integrated patient-centered care and prevention; 2) bold policies and support systems; and 3) intensification of research and incorporation of new technologies.

The pillar of research and innovation in the Global TB Elimination Strategy should prioritize research through a continuum from fundamental/translational research to the discovery and development of new products (vaccines, drugs, inputs, and management strategies), linked to the operational/implementation and health system research that analyze the impact of incorporating new products into the public and/or private healthcare system.

The promotion of Pillar 3 (Research) in the Global TB Elimination Strategy was emphasized in the Global Action Framework for TB Research[19,20]. This framework prioritized the establishment of national TB research networks, similar to the Brazilian TB Research Network (Rede TB)[39], and foster the research interaction among national researchers from different disciplines, institutions involved in TB product development and innovations, and national and international funders.

In Brazil, favorable results in the decentralization of TB control actions for primary care have been described, through secondary data, at the national level[40]. However, in studies conducted in capitals[41], or through local primary data, where managers, health professionals, and users of the health system were interviewed, the results are not homogeneous[42-44].

However, the TB incidence and proportion of TB treatment completion were higher in municipalities with high family allowance coverage (Bolsa Família Program), even in municipalities with a high proportion of DOTS or coverage of the Family Health Strategy.[15-16] These results need to be confirmed elsewhere, but corroborate the importance of the adoption of Pillar 2 (social protection) in conjunction with Pillar 1 (integrated and patient-centered care) and Pillar 3 (research and innovation) for TB elimination, as proposed in the 2015 National TB Research Agenda for Brazil in 2015[45].

Brazil participated actively in the construction of Pillar 2 with the largest income transfer program worldwide, the Bolsa Familia Program. Therefore, pragmatic studies should be fostered with new approaches on social protection to identify which interventions are most effective and best for TB patients and their families.

Facing the complexity of factors that interfere with the TB control, the Rich proposal that equated the pathogenesis of an infectious process (at the individual level) was computed using the following mathematical expression:

$$P = \frac{\mathrm{N.V.H.}}{\mathrm{R\,(n + a)}}$$

where N is for the number of bacilli; V for virulence; H for human hypersensitivity; Rn for natural resistance; and Ra for acquired resistance, following the biomedical logic.

A holistic innovative approach for TB elimination was proposed by Ruffino-Netto[46] through the expression:

$$CTb \approx \frac{(DSOC).(PHIV).(PABT).(PR).(MMIG).(EPOP)}{(DOSS).(DOT).N\,(EDU + NUT).(RHSS).(GPP)}$$

where CTb: tuberculosis burden; DSOC: social inequality; PHI: prevalence of HIV/AIDS; PABT: percentage of treatment abandonment; PR: prevalence of drug-resistant TB cases (primary or acquired); MMIG: migratory movements; EPOP: aging of the population; DOSS: availability of service organization; DOTS: prevalence of directly observed treatment strategy; N (EDU + NUT): educational and nutritional levels of the population; RHSS: adequate and well-prepared human resources in health services; and GPP: degree of political involvement of the population.

This approach would help in the inclusion of research and social protection as a new approach to be pursued at TB control programs at national, regional, and local levels.

In addition, in the recent years, in countries with low TB burden and those with high TB burden [Brazil, Russia, India, China, and South Africa (BRICS)], the irremovable need for interaction between the academy, government, and industry has become a consensus among researchers in basic, translational, clinical and operational areas[39].

These countries significantly focused on the capacity of researchers and organizations to promote internal innovations in parallel to the incorporation of externally produced scientific and technological knowledge[47]. As recently, scientific development (manuscripts in indexed journals, doctoral tests, or master's dissertations), coupled with the technological development of products (medicines, vaccines, and diagnostic supplies) in an isolated way, is not beneficial to the society.

The degree of safety and efficacy of these products should be confirmed through clinical research in explanatory clinical trials (those aimed at obtaining registration with regulatory bodies), as well as the high effectiveness and efficiency in pragmatic clinical trials (those who analyze the clinical and budgetary impact on patients and the local health system) through operational/implementation research[12,20,35-37].

Recently, in order to speed up the interaction between the academia, industry, and government, the Rede TB has been promoting, in close collaboration with the National Tuberculosis Control Program, innovative and strategic activities in TB Research[39,45].

TB elimination in Brazil, a country with a continental dimension and enormous socioeconomic and operational diversity, reinforces the need for intersectoral actions conducted at different levels of healthcare, in order to converge efforts and to achieve the goals of the Brazil Plan for TB Elimination launched by Ministry of Health, in 2017[48]. Considering the relevance of incorporating research into the Global and National TB Elimination Plans, the Rede TB has advocated for the strengthening and/or identification of centers to train health professionals and to develop and conduct research that may contribute to the generation of evidence and improvement of programmatic recommendations. In addition, the capillarity of its researchers throughout the national territory integrated into the tuberculosis programs could result in a greater specificity of the interventions evaluated, thus allowing the recommendations to be refined to the local epidemiological context.

Faced with the urgency of TB elimination, funders, researchers, managers, health professionals, industry representatives, and the civil society should be synergistically organized and aligned in the selection of the best clinical, basic, and translational research, quality, and completeness of care for TB subjects.

Conflict of interest

The authors declare that there is no conflict of interest.

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