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Treatment of Tuberculosis in Brazil—Past, Present, and Future Challenges

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Abstract

Purpose of review Almost 75 years since the introduction of chemotherapy for the treatment of tuberculosis (TB), it remains the single leading infectious cause of mortality and one of the top 10 causes of deaths in 2016 worldwide. Brazil is one of the countries with the highest burden of disease in the world, and despite the downward trend in disease incidence and mortality, TB is still the third leading cause of death among infectious diseases in the country. Although diagnosis and treatment are performed universally and free of charge, barriers in access result in 69,500 new cases and 4500 deaths each year. This review provides a historical overview and the latest knowledge of TB treatment and adherence optimization in Brazil.

Recent findings Chemotherapy remains the main component of the arsenal used to control TB. The currently available treatments can cure almost all TB cases with a timely diagnosis; however, failing to complete prescribed therapy can lead to poor outcomes, including increased risk of treatment failure, disease relapse, sustained transmission, development of drug resistance, and ultimately death. Adherence is a complex and challenging key element for treatment success. Thus, several intervention strategies to improve compliance have been used during the last several decades of TB treatment. Among the most used and recommended by the World Health Organization, fixed dose combinations and directly observed therapy are discussed in detail.

Summary New drugs and shorter regimens may constitute the main treatment for drug-sensitive and MDR-TB in the future. Increasing access to rapid automated nucleic acid amplification tests and culture of sputum are key elements for diagnosis and management of MDR-TB. Treatment descentralization, the incorporation of directly observed therapy to the Family Health Strategy, fixed dose combinations, and non-financial incentives are among options used by the Brazilian Ministry of Health for improving compliance.

Introduction

Tuberculosis (TB) is one of the oldest communicable diseases in humanity. Almost 75 years since the introduction of chemotherapy for the treatment of TB, it remains the single leading infectious cause of mortality and one of the top 10 causes of deaths in 2016 worldwide [1–3]. TB treatment involves taking multiple medications daily for months to years, depending on the level of drug resistance. The currently available treatments can cure almost all TB cases with a timely diagnosis; however, failing to complete prescribed therapy can lead to poor outcomes, including increased risk of treatment failure, disease relapse, sustained transmission, development of drug resistance, and ultimately death.

As part of the World Health Organization (WHO) global effort to reduce the TB incidence and mortality coefficients, the Brazilian Ministry of Health (MoH) developed a national plan to end TB as a public health problem in Brazil, reaching the goal of < 10 cases and < 1 death per 100,000 inhabitants by the year 2035 [4, 5]. Brazil has a relevant role in addressing TB in the Americas, and despite sharing some characteristics common to the region (such as a high rate of urbanization, great social inequality, and ethnic and cultural diversity), it has some characteristics that help to understand the capacity of the Brazilian response to the TB problem: it has the 2nd largest Gross Domestic Product in the Americas, second only to the US; has the 5th highest per capita income in South America; has the 6th highest life expectancy among the Latin American countries; ranks 15th in the ranking of the Human Development Index among the American countries [6].

Brazil is one of the countries with the highest burden of disease in the world, and despite the downward trend in disease incidence and mortality (Fig. 1), TB is still the third leading cause of death among infectious diseases in the country [1, 8]. Although diagnosis and treatment are performed universally and free of charge by the Brazilian Unified Health System (*Sistema Único de Saúde*; SUS [9]), barriers in access result in 69,500 new cases and 4500 deaths each year [8, 10•]. Large urban centers, such as the city of São Paulo and other capitals, are the main responsible for the magnitude of this disease in the country. In such settings, poverty clusters, high-risk groups (prison population, indigenous people, sheltered population, people living with HIV/AIDS (PLHIV/AIDS)), and the non-execution of adequate control actions contribute to this scenario [11].

Tuberculosis in Brazil—a brief overview

Paleopathological research suggests that the first cases of human involvement by *Mycobacterium tuberculosis* occurred at least 5000 years BC, where records of vertebral involvement (Pott's Disease) and tissues of Egyptian mummies containing the DNA of the bacterium were dated from this time [12]. In the New World, archeological findings point to the presence of pulmonary TB in a Peruvian mummy dating to 1100 BC. However, it is proposed that TB has assumed an epidemic condition in the indigenous population (and especially in Brazil) only after contact with European explorers and conquerors [12, 13].

The permanent contact of the Brazilian Indians with the Jesuits and colonists infected by the "white plague" caused sickness and death of many natives. It is suggested that Manuel da Nobrega and José de Anchieta, (Portuguese Jesuits priests who arrived in Brazil around 1549 and established the city of Sao Paulo), were the first individuals to be known to be a carrier of TB and killed by the disease in the country [14]. The tuberculosis epidemic increased in large Brazilian cities during the nineteenth century, like other large European cities during urbanization and the industrial revolution. Brazilian estimates of 1855 suggest a TB mortality of 700 cases per 100,000 inhabitants [15].

The Brazilian fight against TB began in 1889 with the creation of "Leagues Against Tuberculosis" which prioritized the construction of sanatoriums and dispensaries. During this period, public health was managed in line with the

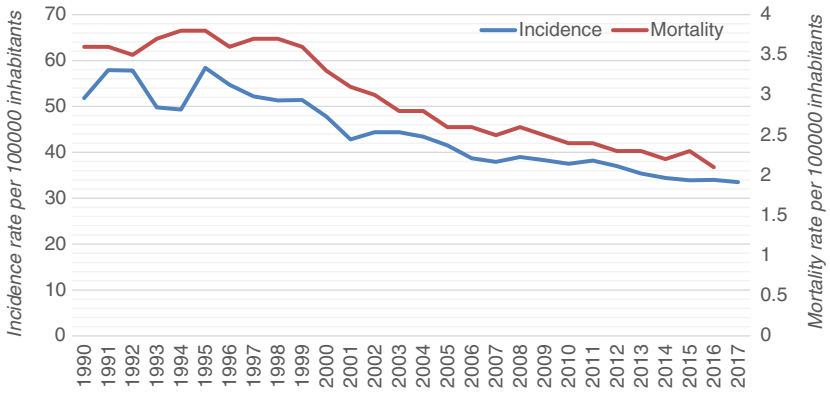

Fig. 1. Historical rates of tuberculosis incidence and mortality [7].

economic and political interests of the local elite, while the economically disadvantaged population received medical assistance from philanthropic entities linked to the Catholic Church, especially the Santa Casas de Misericordia (Holy Houses of Mercy) [16, 17]. These had a pioneering supportive role in the care of TB patients since colonial Brazil until the early 1920s [18].

However, the disease continued to plague the Brazilian society despite the modest successes of the sanatorium approach and the variable efficacy of the newly developed BCG vaccine, in the early and mid-1900s [19]. Marked as one of the main causes of death in the Brazilian capitals, TB was responsible for estimated 10% of the deaths occurred in the city of São Paulo throughout the first half of the twentieth century [20]. It was only in the 1960s that notable achievements toward the control of the disease were obtained: mandatory BCG vaccination, inclusion of TB among diseases of compulsory notification, assurance of free means of prevention, diagnosis and treatment, expansion of the treatment to the less populated regions of the country, rehabilitation of infected patients, and stimulation of scientific research [11].

The following decades were marked by successful control of the disease, with reductions in the number of cases of 2% to 4% per year. At that time, treatment was carried out exclusively in the Basic Health Units, and old sanatoriums were transformed into hospitals, where hospitalizations occurred only in selected cases. The decentralization and municipalization of public health policies—considered a revolutionary step towards universal TB treatment especially in such continental country—were only achieved after the creation of SUS in 1988 [9]. However, since the early 1990s, the impact of the HIV/AIDS epidemic, the deterioration of socioeconomic conditions, insufficient funding, and the disruption of health systems (poor infrastructure and inadequate human resources), especially in large cities in developing countries [21], led to an alarming increase in the number of TB cases in Brazil and worldwide, which led the WHO to declare TB a global health emergency in 1993 [22].

Brazil has figured the WHO's *High burden country* (HBC) list since its creation in 1998 [23]. By the end of 2015, a revisited classification was defined to address the disease globally and three new HBC lists have been established (TB burden, TB/HIV coinfection, and MDR-TB (multidrug-resistant TB)), totaling 48 priority countries. Brazil is the only country in the Americas to be included as *Top 20* in two lists, ranking 20th in disease burden and 19th in TB-HIV coinfection [1]. The country is also notable for its participation in the BRICS (a

bloc formed by Brazil, Russian Federation, India, China, and South Africa), high-burden countries responsible for more than 50% of TB cases in the world and mobilization of > 90% of the resources needed for TB control actions through domestic sources of funding [1].

Antimycobacterial therapy

Chemotherapy remains the main component of the arsenal used to control TB. Before the introduction of the first antimicrobial agents, TB management relied basically upon high-quality assistance, bed rest, dietary intervention, heliotherapy (exposure to sunlight), aerotherapy (fresh air and mountain climate), moderate exercising, and herbal poultices [24, 25•]. Since 1944, the introduction of streptomycin and para-amino-salicylic acid (PAS)—later augmented by isoniazid in 1951—played a decisive role in controlling endemic TB [24]. However, the emergence of bacterial resistance led to the necessity of prolonged courses multidrug therapy, usually given as triple therapy and for 24 months. In the 1960s, the current second-line drugs in TB treatment were identified, and the duration of treatment was reduced to 18 months. During the following decades, Brazil was a key country in shorter regimen clinical trials. This period was marked by further reductions of the duration of treatment after the introduction of rifampicin (from 18 to 9 months) and pyrazinamide (from 9 to 6 months) [26]. Such antibiotics showed potent bactericidal activity when associated with isoniazid, and therefore made the implementation of short-course chemotherapy possible [27].

The former *Scheme I* combined rifampicin, isoniazid, and pyrazinamide (RHZ) and is considered one of the foundations of TB control strategies worldwide since the late-1970s. In 1979, Brazil became the first developing country to standardize the 6-month regimen with oral RHZ provided by a public health service network, free of charge and, more recently, under supervision [11] (Table 1). Despite a history of remarkable scientific achievements in therapeutics and after more than 30 successful years of TB control in Brazil, the apparently solved problem of drug resistance was resuscitated in Brazil and

Table 1. Therapeutic schemes and their respective duration and year of implementation, adopted as the standard treatment of TB in Brazil, since the discovery of streptomycin

Year	Therapeutic regimen	Duration (months)
1944	Streptomycin	24
1948	SP	24
1952	SH	18
1964	SHP	18
1965	3SHP/3HP/6H	12
1971	3SHT/9HT	12
1979	2RHZ/4RH	6
2009	2RHZE/4RH	6

S streptomycin, *H* isoniazid, *P* para-amino salicylic acid (PAS), *T* tiacetazone, *Z* pyrazinamide, *R* rifampicin, *E* ethambutol
Adapted from [18]

Table 2. Dosage schedule for FDCs of WHO-recommended strengths for children and adults

Patient's body weight (kg)		Initial phase: 2 months		Continuation phase: 4 months		6 months
		RHZE daily	RHZ daily	RH daily	RH ×3 weekly	EH daily
≤ 7	Strength for children	–	1	1	1	–
8–9		–	1.5	1.5	1.5	–
10–14		–	2	2	2	–
15–19		–	3	3	3	–
20–24		–	4	4	4	–
25–29		–	5	5	5	–
30–37	Strength for adults	2	2	2	2	1.5
38–54		3	3	3	3	2
55–70		4	4	4	4	3
≥ 71		5	5	5	5	3

R rifampicin, *H* isoniazid, *Z* pyrazinamide, *E* ethambutol
Adapted from [46]

worldwide in the 1990s under the AIDS epidemics and the devastating interaction between HIV and *M. tuberculosis* [21]. Consequently, in 2009, Brazil added ethambutol as the fourth drug in the intensive treatment phase given as fixed dose combination (FDC), due to the increasing rates of primary isoniazid resistance (from 4.4 to 6.0%) [28, 29] (Fig. 1).

Treatment of latent TB infection

Several regimens are used for the treatment of LTBI, which is also considered a key part of the End TB Strategy [30, 31, 32•]. The 6-month course of isoniazid is currently recommended by the Brazilian MoH as the standard treatment, which can be prolonged to 9 months in people living with HIV and those with selected immunosuppressive conditions [33]. However, in light of recent studies on shorter regimens and their association with increased adherence rates and reduced hepatotoxic effects [34, 35], abbreviated treatments are expected for the next few years in Brazil.

Treatment of drug-sensitive TB in Brazil

In patients with drug-susceptible pulmonary and non-meningo-encephalic extrapulmonary TB (independently of HIV infection status, disease recurrence or previous treatment abandonment), the 6-month rifampicin-based regimen is the recommended *basic regimen*, since cure rates have remained over 90% over the last 30 years [36••, 37] (Tables 2 and 3). For meningo-encephalic TB, the second phase (also called *maintenance phase*) is extended to 7 months, and systemic glucocorticoids are administered for 4 to 8 weeks, followed by a 4-week period of drug tapering.

Table 3. Recommended regimens according to the patient's treatment situation and health care units

Situation	Recommended regimen	Treatment administration site
LTBI	6H	Basic health care units
New extrapulmonary case	2HRZE/4HR (*basic regimen*)	Basic health care units
New meningo-encephalic case	2HRZE/7HR	Hospital treatment ➔ tertiary reference centers
Disease recurrence after cure or treatment resumption after abandonment	2HRZE/4HR until sensibility tests results.	Basic health care units ➔ tertiary reference centers (depending on sensibility tests results)
Special treatments: chronic hepatopathies, major side effects, HIV/AIDS, and immunosuppression.	Special treatments	Secondary reference centers
Treatment failure secondary to mono-resistance or multidrug-resistant	Special treatments	Tertiary reference centers

LTBI latent tuberculosis infection, *R* rifampicin, *H* isoniazid, *Z* pyrazinamide, *E* ethambutol
Adapted from [33]

In individualized cases, treatment is provided at tertiary reference centers and may be prolonged up to 7 months in maintenance phase according to the clinical-radiological evolution during treatment (Table 3). Cavitary forms, those who remain with positive smear microscopy at the end of the second month of treatment, evidence of monoresistance to rifampicin or isoniazid and PLHIV/AIDS are among such selected cases. Fluoroquinolone containing regimens and 4-month standard regimens (occasionally considered for minimal disease, sputum smear, and culture-negative cases [38]) are not recommended for drug-sensitive TB by the Brazilian MoH. The former approach could lead to overall savings from both SUS and patient perspectives [39].

Treatment of drug-resistant TB in Brazil

Despite the rising rates of MDR-TB, such levels remain low compared to other countries, such as India, China, and the Russian Federation, which account for almost 60% of cases of multidrug-resistant TB in the world [40]. MDR-TB and extensively drug-resistant tuberculosis (XDR-TB) treatments are standardized by the Brazilian MoH and WHO recommendations and are managed exclusively at tertiary reference centers [41].
Patients with rifampicin resistance (RR-TB) or MDR-TB should not be eligible for the shorter regimen. Hence, at least five active TB medicines should be used during the intensive phase (including RHZ) plus four *core second-line agents* (one chosen from group A, one from group B, and at least two from group C). If the minimum of effective TB medications cannot be composed as described above, an agent from group D2 and other agents from group D3 (so-called *add-on agents*) should be added to bring the total to five (Table 4).

Special situations

Treating TB during pregnancy, in newborns, individuals with chronic liver disease or chronic nephropathies, and immunosuppression can be

Table 4. WHO classification of anti-tuberculosis drugs: comparison between WHO 2014 and 2016 guidelines [41, 73]

WHO 2014		WHO 2016			
Group	**Drugs**	**Group**		**Drugs**	
Group 1	Isoniazid	First-line oral agents		Isoniazid	
	Rifampicin			Rifampicin	
	Ethambutol			Ethambutol	
	Pyrazinamide			Pyrazinamide	
	Rifabutin, rifapentine			Rifabutin, rifapentine	
Group 2	Streptomycin	Group A[a]: fluoroquinolones	Core second-line agents	Levofloxacin	
	Kanamycin			Moxifloxacin	
	Amikacin Capreomycin			Gatifloxacin	
Group 3	Levofloxacin	Group B: second-line injectable agents		Amikacin	
	Moxifloxacin			Capreomycin	
	Gatifloxacin			Kanamycin (streptomycin)[b]	
Group 4	Ethionamide	Group C[a]: other core second-line agents		Ethionamide/prothionamide	
	Prothionamide			Cycloserine/terizidone	
	Cycloserine			Linezolid	
	Terizidone *p*-Aminosalicylic acid			Clofazimine	
Group 5	Bedaquiline	Group D	Add-on agents (not part of the core MDR-TB regimen)	D1	Pyrazinamide
	Delamanid				Ethambutol
	Linezolid				High-dose isoniazid
	Clofazimine			D2	Bedaquiline[c]
	Amoxicillin/clavulanate				Delamanid[d]
	Imipenem/cilastatin			D3	*p*-Aminosalicylic acid
	Meropenem High-dose isoniazid				Imipenem-cilastatin (requires clavulanate)[e]
	Thioacetazone				Meropenem (requires clavulanate)[e]
	Clarithromycin				Amoxicillin-clavulonate[e] (thioacetazone)[d, f]

[a]Medicines in groups A and C are shown by decreasing order of usual preference for use
[b]Streptomycin may substitute other injectable agents when the other three cannot be used, but its use has been recently reduced globally
[c]Bedaquiline is available in Brazil for research purposes only
[d]Not available in Brazil
[e]Clavulanate is only available in formulations combined with amoxicillin
[f]HIV negative status required before administering thioacetazone

challenging and is not handled in Basic health care units. Therefore, individuals with such conditions and those facing major side effects are treated in secondary reference centers, where specific regimens are provided for each situation (Table 2) [33]. For PLHIV/AIDS, antiretroviral treatment is also provided by SUS at no cost. Because antiretrovirals and TB drugs have recognized toxicity and require strict adherence, the concomitant onset of both regimens increases the risk of drug intolerance and overlap or potentiation of adverse events, ultimately leading to interruption of the whole scheme.

Drug acquisition in Brazil

Contrasting to other high-burden countries, Brazil produces first-line TB drugs (including FDC formulations) and some second-line TB drugs through a strong network of public pharmaceutical manufacturing laboratories certified by WHO [42]. There is no private market for TB treatment, and the Brazilian MoH delivers treatment to its federative units free of charge. Hence, TB drugs are provided exclusively by SUS, except for quinolones and aminoglycosides, and free of charge to all patients. Such strategy is considered greatly responsible for the relatively low rates of multidrug-resistant TB in the country compared to other high-burden countries [1].

Treatment optimization

Adherence is a complex and challenging key element for treatment success. Running in parallel to chemotherapy, compliance is part of the first pillar of the WHO's End TB Strategy [5]. Globally, several intervention strategies to improve compliance at the health system level have been used during the last several decades of TB treatment, but it is still unclear which are most effective [43•, 44]. Two of them will be discussed in more details.

Fixed dose combinations

Since multidrug chemotherapy is one of the cornerstones of the current approach to the control of TB, the use of FDCs (defined as a formulation of two or more biologically active substances, combined in a single drug, and available at certain fixed doses) simplifies treatment and drug management, hence providing a more convenient form of administration [31, 45••]. Additionally, by reducing the number of tablets to be ingested daily in up to 80%, FDCs decreases the probability of treatment failure secondary to monotherapy (especially in the initial phase of treatment), reduces single drug unavailability, decreases prescription errors by dosage miscalculation, and improves both drug supply and distribution systems [46].
Brazil is one of the oldest manufacturers of R and H, produced since the 1970s. In 2009, RHZE was adopted as the standard regimen for new cases of drug-sensitive TB (Tables 1 and 3). For this, transfer of technology and new systems for quality control and pharmacovigilance were necessary for further national production—which has not yet reached self-sufficiency. Despite the unquestionable benefits of FDC for the patient, such modifications took Brazil from the comfortable position of self-sufficiency to the condition of a major international buyer of medications, and therefore susceptible to the risk of shortages of essential tuberculostatic drugs.

Directly observed therapy

After 1993 WHO's declaration, directly observed treatment (DOT) was recommended throughout the entire course of therapy [47, 48]. It was originally developed in the 1970–1980s and appeared to be a solution to

reduce noncompliance and abandonment of treatment [49]. Briefly, in DOT, medication uptakes are observed at home (by family members or community health agents) or health facility (by health workers). Such strategy targets to increase patient adherence through supervised treatment, regular collection of sputum specimens (until two consecutive samples test negative for acid-fast bacilli), and patient-centered support [50].

FDC and DOT strategies should be used concomitantly, as treatment failure and drug resistance can occur secondary to both inadequate doses and recurrent interruption of treatment [51]. The optimal dosing frequency for new patients with TB is daily throughout therapy (i.e., 7 days/week). However, the administration of medications on business days only, or intermittently (i.e., 3 days/week) may facilitate in-person DOT [52].

Since the launch of the Brazilian Emergency Plan for Tuberculosis Control in 1996, the MoH incorporated DOT to the Family Health Strategy (FHS)—SUS innovative and scaling up community-based approach to provide universal primary health care through interdisciplinary teams [10]. FHS relies on community health agents (paid lay members of the local community who are part of the health care team) to improve the team access to the population. Observed treatment is universal in Brazil, contrasting to other countries that use such strategy for those with sputum smear-positive pulmonary disease (who are most likely to transmit the disease). Despite labor intensive, combining DOT and FHS strategies is considered an efficient, cost-effective, and patient-centered core strategy for TB control, resulting in an increase of the supervised treatment coverage from 3% to approximately 36% in the last decade in Brazil [8, 53, 54].

Non-financial incentives (such as free snacks during DOT, food aid, and free transportation) have been successfully used in Brazil for almost two decades in almost 45% of the priority municipalities [55]. Such approaches are based on an assessment of the individual's socioeconomic status and for those with reduced access to health care centers.

TB diagnostics and the impact in treatment

Timely and accurate diagnosis is essential for early treatment initiation, interruption of the transmission chain, rapid identification of resistant forms, and better outcomes. In such a wide territory and with diverse economic, social, and health care realities, some states of Brazil are marked pioneer in TB control policies. The State of São Paulo, for example, is responsible for more than 20% of the annual TB cases in Brazil. Therefore, it was the first state to promote annual campaigns for the active search for TB cases, which act at all municipalities and in all its prison system twice yearly. Following some of the successful efforts of the São Paulo State, the Brazilian MoH adopted several public actions to increase awareness and facilitate the access to treatment. Non-monetary awards are used as positive reinforcement for the municipalities and States that reach the national goals and financial benefits for each case of registered cure are offered by some municipalities. Free online and in-class courses for the management of TB in the most

vulnerable populations, aimed at the health professionals of primary care centers and prison staff, are in final stages of elaboration by the MoH and will deliver updated information to those in close contact to priority TB patients.

The Brazilian MoH has launched national TB campaigns adapted to the Brazilian setting, using a locally famous singer and a world known Brazillian footballer as TB ambassadors. Their high popularity and real-life history (both made public their TB diagnosis and curative treatments) helped to inform people through social media [56]. Several awareness campaigns have been used at mass events held in the country, including carnival (annually), the XXVIII World Youth Day (2013), and the FIFA Confederations Cup (2013). The "Dribbling tuberculosis" campaigns aimed to increase the visibility of the disease through health education activities for children and included soccer players from national teams to increase awareness of the disease during the 2010 and 2014 FIFA World Cups. Such approaches can be useful when adapted to other high-burden countries with shared populational characteristics.

Brazil has also engaged efforts to improve its laboratory network, increase access to rapid automated nucleic acid amplification tests (NAATs), and develop the local production of PPD (purified protein derivative), therefore strengthening the TB control actions [57]. Direct sputum smear microscopy is a fundamental tool in adults, both for the diagnosis of pulmonary TB and for treatment control. In Brazil, such method is routinely performed and widely available at the municipal level, but since children under age of 10 are rarely bacilliferous, the Brazilian MoH recommends a clinical-radiological scoring system to support the diagnosis of pulmonary TB in HIV-negative children [33, 58].

More recently, NAAT has constituted a new pillar in the diagnosis of pulmonary and extrapulmonary TB. GeneXpert® MTB/RIF assay (Cepheid Inc., Sunnyvale, CA, USA) is the most used fully automated cartridge-based real-time DNA-based test that can detect both TB and resistance to rifampicin in less than 2 h. It has been recommended by WHO for pulmonary, extrapulmonary, and pediatric TB since 2010 [59]. It was introduced in Brazil in priority municipalities in 2013, which increased the detection of new TB cases by 43% compared to smear microscopy [57]. Though still not universal, its implementation has dramatically increased during the last 5 years, making Brazil the 3rd leading country procuring GeneXpert cartridges worldwide [60].

Another key element for diagnosis and management of MDR-TB is culture of sputum. Since not universally available in all Brazilian federative units due to logistic and laboratory limitations, culture is indicated for selected situations [33]: individuals with previous treatment (regardless of the time elapsed between cases), anti-TB treatment failure, immunosuppressed patients (particularly PLHIV/AIDS), and populations at higher risk of harboring resistant *M. tuberculosis* strains (close contact with TB-MDR/XDR cases, health professionals, street dwellers, prison staff, and inmates). Unlike other Brazilian states, the state of São Paulo also performs culture in all the samples with the identification of antibiotic resistance by GeneXpert.

Lastly, the tuberculin test, used for the diagnosis of LTBI in all age groups and a particularly important supporting method for the diagnosis of active disease in children [61•], has faced recurrent shortages worldwide within the past several years. To circumvent this situation, the

Brazilian MoH is evaluating a national PPD production program and the incorporation of interferon-gamma release assay technologies (IGRAs) to its TB program [55, 62].

Conclusion

Despite its accomplishments in reducing poverty, hunger, and TB incidence and mortality in the last decades, SUS faces severe financial and organizational challenges, which worsened after the severe economic and political crises that began in 2014 [63]. Such a situation can trigger cascades of events that adversely affect SUS and the National TB Program, ultimately putting the country a little further away from reaching the End TB Strategy goals.

However, regardless of this volatile scenario, Brazil has accumulated several victories against TB along the trajectory of the National Tuberculosis Control Program. The country has increased its investment in scientific and technological innovation [64] and has become a member of an innovative group of HBC that have incorporated research into their TB control programs, as part of the third pillar in the WHO End TB strategy [5]. Additionally, the Brazilian Tuberculosis Research Network (REDE-TB) has played a key role in the creation of the BRICS TB Research Network and has obstinately encouraged the inclusion of TB in the Brazilian national political health agenda. Therefore, the development of new TB drugs, technologies, and production platforms are now considered research priorities in Brazil [65, 66].

More recently, pediatric FDCs (produced as dispersible tablets as well as powder) are being developed locally in collaboration with the Global TB Alliance and are expected to incorporate the already WHO-prequalified FDC regimens for children [66–68]. Bedaquiline and delamanid became available in 2013 and 2014, respectively, for MDR-TB treatment [41] and shorter promising regimens composed of fluoroquinolones and pyrazinamide have been studied. Such new regimens may constitute the main treatment for drug-sensitive, MDR-TB and XDR-TB in the future. Yet, only bedaquiline is available in Brazil and under investigational protocols (Table 3) [69••].

Other options for improving compliance evolved along the recent technological revolution and included direct phone calls, short message service (SMS) technology, and electronic pill boxes [43•, 44]. More recently, video (or virtually)-observed therapy (VOT) has gained attention as an alternative mode of delivering DOT, by reducing perceived stigma related to DOT and both patient-level and program-level costs [52, 70–73]. However, despite promising, these options often face technological and economic barriers in a country of continental dimensions like Brazil.

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Compliance with Ethical Standards

Conflict of Interest
The author declares that he has no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Human and Animal Rights and Informed Consent
All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Publisher's Note

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
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- •• Of major importance

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