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REVIEW ARTICLE

Management of multidrug-resistant tuberculosis: main recommendations of the Brazilian guidelines

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ABSTRACT

Over the years, various recommendations have been made in pursuit of controlling resistance to antituberculosis drugs, especially multidrug resistance, in Brazil. Given the importance of standardizing those recommendations, the aim of this study was to describe the main recommendations of the Brazilian guidelines, primarily those related to the treatment and follow-up of cases of tuberculosis. From August through October of 2018, a document search was conducted via the websites of the Brazilian National Ministry of Health, the Brazilian National Tuberculosis Control Program, the JBP, and the Official Gazette of the Federal Republic of Brazil. Data were collected systematically by using a protocol designed specifically for this study. Documents published between 2004 and 2018 were selected. It was possible to understand and trace the history of the measures for the control of multidrug-resistant tuberculosis in Brazil from 2004, when the first documents related to the disease were published, up to 2018, when the second edition of the Brazilian National Guidelines for the Control of Tuberculosis was published. The contents of the documents were analyzed and grouped by case definition, diagnostic criteria, treatment, use of directly observed treatment; mechanisms of social protection for patients; data tools; and organization of care. This analysis allowed us to understand the efforts towards standardizing some measures in Brazil, not only identifying advances in the alignment with international prerogatives (case definition, incorporation of diagnostic technology, and treatment regimens) but also underscoring the need for greater clarity regarding the mechanisms of social protection and the organization of the care provided via the Brazilian health care system.

Keywords: Tuberculosis, multidrug-resistant; Organization and administration; Practice patterns, physicians'; Practice patterns, nurses'.

INTRODUCTION

Drug-resistant tuberculosis (DR-TB)—tuberculosis that is resistant to drugs used in the treatment of tuberculosis—poses a serious threat to attempts to control tuberculosis worldwide.[1] Multidrug-resistant tuberculosis (MDR-TB) is defined as that which is resistant to both rifampin and isoniazid, whereas extensively drug-resistant tuberculosis (XDR-TB) is defined as that which, in addition to being resistant to rifampin and isoniazid, is resistant to a fluoroquinolone and a second-line injectable drug; these are the most worrying forms of tuberculosis.[2]

Another form of DR-TB that is a major concern is rifampin-resistant tuberculosis (RR-TB), given that approximately 82% of RR-TB cases are also resistant to isoniazid.[3,4] According to the World Health Organization (WHO), there were an estimated 558,000 new cases of MDR/RR-TB and an estimated 230,000 deaths from MDR/RR-TB worldwide in 2017.[1] In 2017 in Brazil, there were 1,119 laboratory-confirmed cases of MDR/RR-TB, 746 of which had started treatment, and 26 laboratory-confirmed cases of XDR-TB, all of which had started treatment.[1]

The WHO has been working to keep a systematic record of the occurrence of DR-TB worldwide,[1] as well as setting clear objectives to address this problem: prevent the emergence of drug-resistant forms through adequate treatment of drug-susceptible forms; expand the network for rapid testing for the timely identification of drug resistance; ensure immediate access of drug-resistant cases to treatment; prevent transmission; and ensure political and financial commitment to fight DR-TB.[1]

In Brazil over the years, some recommendations have been made on the basis of international documents

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and the experience of specialists working in the country.[5] The aim of this study was to describe the main recommendations of past and current Brazilian guidelines on DR-TB care, primarily those related to the treatment and follow-up of cases.

METHODS

A document search was conducted of official Brazilian documents that guide MDR-TB care in the country. The search was conducted via the websites of the Brazilian National Ministry of Health (NMH), the *Programa Nacional de Controle da Tuberculose* (PNCT, Brazilian National Tuberculosis Control Program), the JBP, and the Official Gazette of the Federal Republic of Brazil. The document selection process occurred between August and October of 2018.

For the document review, a protocol was designed based on the results of a recently published integrative review of the literature[6] and the WHO guidelines on MDR-TB care.[7-9] The aspects addressed were as follows: capability/need for communication between levels of care; standardization of practices related to referrals; outpatient care; return visit schedules; capability/need for provision of social, economic, and emotional support to patients undergoing treatment, as well as ways of effecting that; capabilities and involvement of various health care facilities, with a focus on patient and information flow via the Brazilian Unified Health Care System; and adoption of and recommendations on pharmacological treatment regimens.

Documents were read in full, and data related to the aspects addressed by the protocol were extracted by two researchers, working independently, and then compared. A researcher other than those two performed the role of third reviewer when there was divergence between the two sets of extracted information. In the subsequent phase of the study, the data were analyzed, grouped by key themes and concepts, and summarized.

A search of selected sources resulted in the analysis of the following documents: the Second Brazilian Consensus on Tuberculosis: 2004 Brazilian Guidelines on Tuberculosis[10]; the 2007 Guide for Epidemiological Surveillance of Multidrug-Resistant Tuberculosis[11]; the 2009 Technical Note on Changes in the Treatment of Tuberculosis in Brazil for Adults and Adolescents[12]; the (2009) Third Brazilian Thoracic Association Guidelines on Tuberculosis[13]; the 2011 Brazilian National Guidelines for the Control of Tuberculosis[14]; NMH Technical Memo no. 9, in 2014[15]; NMH Technical Memo no. 8, in 2016[16]; and the 2018 Brazilian National Guidelines for the Control of Tuberculosis.[17] A review of the bibliographic references of those eight documents led to the inclusion of a 2007 study on MDR-TB[18] in the analysis, resulting in a final sample of nine documents.

The analysis made it possible to understand and trace the history of the measures for the control of MDR-TB in Brazil from 2004, when the first documents related to the disease were published, up to 2018, when the second edition of the Brazilian National Guidelines for the Control of Tuberculosis was published.[17] The key milestones in this regard are depicted in Figure 1.

ANALYSIS OF DOCUMENTS

The analysis of documents resulted in the division of results into two categories, which are discussed below.

History of the measures for the control of multidrug-resistant tuberculosis in Brazil

The establishment of short-course (6-month) treatment regimens in 1979, standardized by the PNCT, is a major milestone in tuberculosis control in Brazil.[19] The first-line basic regimen, known as regimen I, included a 2-month intensive phase of rifampin, isoniazid, and pyrazinamide (2RHZ), followed by a 4-month continuation phase of rifampin and isoniazid (4RH). This regimen was recommended for treatment-naive patients and for patients who discontinued treatment for < 30 days. For patients who discontinued treatment for > 30 days and for patients who experienced recurrence, regimen I boosted with ethambutol (2RHZE/4RH) was recommended. For patients with meningoencephalitis, the duration of treatment was extended to 9 months: 2RHZ/7RH. For patients who experienced clinical and bacteriological treatment failure, regimen III, which consisted of 3 months of streptomycin, ethambutol, ethionamide, and pyrazinamide, followed by 9 months of ethambutol and ethionamide (3SEEtZ/9EEt), was recommended.[5,10,14,20] However, at health care facilities, there remained patients who did not achieve cure after the standard treatments, cases known as cases of chronic tuberculosis, probably due to drug resistance.[19]

In the 1980s and early 1990s, several experiments with alternative regimens were conducted in Brazil in an attempt to treat patients who did not respond to the recommended drugs.[18] In 1992, the NMH recognized the lack of reliable data on cases of drug-resistance,[20] and, in 1994, the first two cases of MDR-TB were reported in Brazil.[11] Therefore, the need for conceptualization and classification of cases of drug-resistance in Brazil dates from the early 1990s, and for that purpose at that time, operational and bacteriological aspects related to care in the Brazilian context were considered, resulting in a different definition from the one that was then adopted internationally.[21] That definition was seen as a breakthrough in terms of delineating the problem in Brazil, since it was related to the reality experienced by patients and health care professionals. On the basis of that definition, a nationwide survey conducted in 1995 revealed that there were approximately 1,500 cumulative cases of MDR-TB.[20]

With regard to the broader picture of the efforts against tuberculosis in Brazil, the 1990s were marked by severe setbacks in tuberculosis control policies, with the dismantling of the PNCT at the federal level and the weakening of the coordination of local programs.[22] All of those events impacted negatively on the results

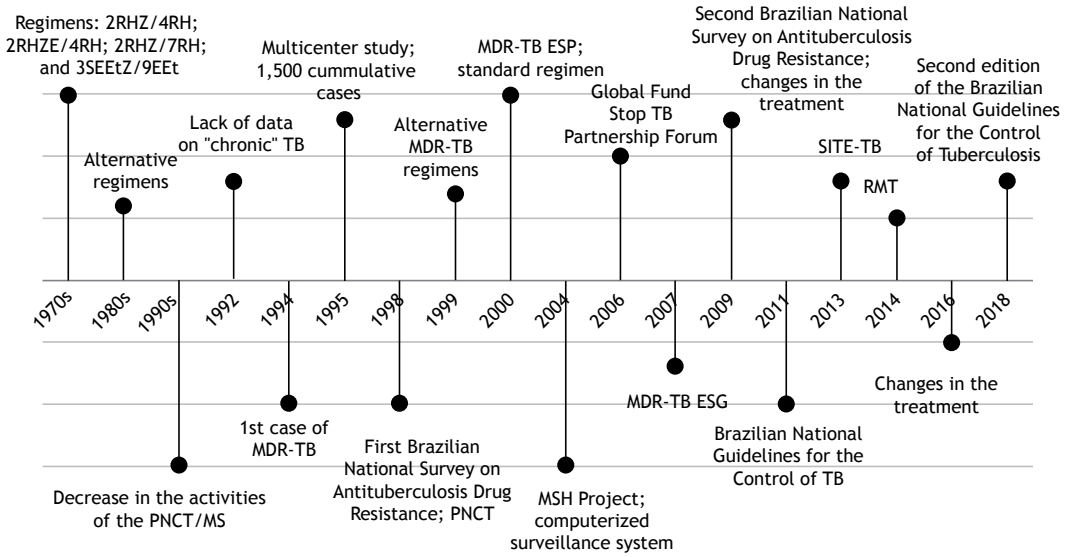

Figure 1. Timeline of milestones in the standardization of practices related to multidrug-resistant tuberculosis in Brazil. Ribeirão Preto, 2019. PNCT/MS: *Plano Nacional de Controle da Tuberculose/Ministério da Saúde* (Brazilian National Tuberculosis Control Program/Brazilian National Ministry of Health); TB: tuberculosis; MDR-TB: multidrug-resistant tuberculosis; ESP: epidemiological surveillance program; MSH: Management Sciences for Health; ESG: epidemiological surveillance guide; SITE-TB: *Sistema de Informação de Tratamentos Especiais da Tuberculose* (Brazilian Database of Special Treatments for Tuberculosis); and RMT: rapid molecular test(ing).

and indicators, which added up to the spreading AIDS epidemic.[23]

Worldwide at that time, there was also a lack of commitment to the problem of tuberculosis, reflected internationally as the occurrence of MDR-TB outbreaks in the United States and the reemergence of the disease as a matter of concern in developed countries in North America and Europe,[20] which was called the "resurgence of tuberculosis" in the northern hemisphere. In developing countries, such as Brazil, the disease has always been "the neglected calamity" that was "ever present and enduring".[23] However, increasing social inequalities, poverty, and a lack of access to goods and services, as well as the growth of the population, an increasing number of people living in urban areas, and the AIDS pandemic, exacerbated the problem of tuberculosis, resulting in increased resistance of the disease to drugs and treatment regimens.[24]

In view of this challenge, in 1995, the NMH *Centro de Referência Professor Hélio Fraga* (CRPHF, Professor Hélio Fraga Referral Center), located in the city of Rio de Janeiro, Brazil, developed a national treatment protocol that was validated through a multicenter study involving the Clemente Ferreira Institute, located in the city of São Paulo, Brazil, the *Hospital Sanatório Partenon*, located in the city of Porto Alegre, Brazil, and the Raphael de Paula Souza Hospital, also located in the city of Rio de Janeiro; this multicenter study was conducted between 1995 and 1998.[11]

The First Brazilian National Survey on Antituberculosis Drug Resistance, conducted between 1996 and 1997, was published in 1998.[20] Concomitantly, all such drugs were registered with the Brazilian National Health Oversight Agency, the purchase of such medications was regulated, and most of such drugs began to be produced by Brazilian public companies.[24] In addition, in a broader context related to disease control measures, a tuberculosis control program was launched; the program addressed the need to provide, free of charge, antituberculosis drugs, including those in special regimens such as regimen III, to patients, as well as to ensure supervised treatment and drug resistance surveillance.[23]

In 1999, the results of a study[20] on the effectiveness of alternative MDR-TB regimens were published in the JBP, providing guidance in the search for standardization of practices, regimens, treatment duration, and the management of cases and outbreaks, as well as of tests and operational aspects that are required for a broad and multidisciplinary approach. In 2000, the proposed regimen was validated by the NMH and an epidemiological surveillance program for MDR-TB was initiated, including case reporting and the consolidation of a database dedicated to this health problem.[11] From then on, the CRPHF began to provide, free of charge, medications for the treatment of all cases of MDR-TB reported in Brazil.[11]

In 2004, a partnership was established with Management Sciences for Health, enabling the continued implementation of epidemiological surveillance systems. The objective of this collaboration between Management Sciences for Health and CRPHF was to improve the reporting system for case follow-up, allowing assessments and searches in the dedicated database, which was then up to date and computerized. In addition, drug shipments and drug stocks were controlled via this database, and the epidemiological

surveillance program for MDR-TB, which has since been computerized, was strengthened and decentralized.[11] The CRPHF became a national referral center, being responsible for drug dispensing, case validation, and the management of the database.[11]

The partnership with Management Sciences for Health also led to the publication of the Guide for Epidemiological Surveillance of Multidrug-Resistant Tuberculosis.[11] This guide allowed the dissemination of standardized recommendations, including diagnosis, pharmacological treatment, case follow-up, prevention, biosafety, database, and human resources, throughout Brazil. The professional and managerial responsibilities and duties of the various actors involved in health care were defined.[5,11,19] In addition, the content of the guide was widely disseminated through refresher courses on MDR-TB, which were offered in all Brazilian states and the Federal District of Brasília.[11]

In 2006, financing was granted by the Global Fund against AIDS, Tuberculosis and Malaria, and this resulted in the creation by the NMH of the "Stop TB Partnership" Forum, which represented an achievement in disease control by officially acknowledging the role of social participation/mobilization.[11,24]

The Second Brazilian National Survey on Antituberculosis Drug Resistance occurred between 2006 and 2008[12]; the survey involved a representative Brazilian sample and sought to determine patterns of resistance to first- and second-line drugs in both outpatient and inpatient follow-up cases.[11,25] Its preliminary results indicated an increase in primary resistance to both isoniazid (from 4.4% to 6.0%) and rifampin (from 0.2% to 1.5%) and led the PNCT to change in 2009 several aspects related to the treatment of tuberculosis in Brazil.[5,14,19]

Also in 2009, the Third Brazilian Thoracic Association Guidelines on Tuberculosis were published.[13] From then on, a "basic regimen", which included the use of ethambutol as a fourth drug in the intensive phase of treatment (for patients aged 10 years and older), was adopted, as were fixed-dose combination tablets.[5,14,19]

All tuberculosis-related guidelines were revised and published in the 2011 Brazilian National Guidelines for the Control of Tuberculosis.[14] There were specific recommendations for confirmed cases of drug-resistance and for early detection of cases of DR-TB.[5,14] However, unlike the Guide for Epidemiological Surveillance of Multidrug-Resistant Tuberculosis,[11] the 2011 guidelines[14] provided general guidance on all forms of tuberculosis, defining drug-resistance and offering the related recommendations in one of the chapters. In addition, the 2011 guidelines provided the definition of cases of and special regimens for DR-TB and nontuberculous mycobacteria, as well as of patient flow through health care facilities and levels of care, establishing secondary and tertiary referral centers.[5,14] In 2013, the database was changed and renamed *Sistema de Informação de Tratamentos Especiais da Tuberculose* (SITE-TB, Brazilian Database of Special Treatments for Tuberculosis).[26]

In July of 2014, the use of a rapid molecular test (RMT)—Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA)—performed on the GeneXpert platform,[26] began to be implemented throughout Brazil. Xpert MTB/RIF is an automated, real-time polymerase chain reaction-based assay that, in approximately 2 h, detects bacillus DNA and mutations that can cause resistance to rifampin.[27,28] The intent of the implementation was to reduce the time to diagnosis of tuberculosis and to optimize early identification of resistance to rifampin, which is in line with the WHO recommendations and the goals of the End TB Strategy.[26,29]

The General Council of the PNCT prepared, discussed, and validated new recommendations in consultation with national and international specialists, on the basis of the WHO recommendations and literature review. A technical memo in which the standard MDR-TB regimen was changed was published in 2016.[7,16] The technical memo also emphasized the need to carry out directly observed treatment (DOT) in partnership with primary health care teams to ensure appropriate follow-up, and the importance of reporting cases to the Brazilian Case Registry Database and SITE-TB.[16]

The last change during the study period is related to the Brazilian National Guidelines for the Control of Tuberculosis, which were disclosed to the members of the Brazilian Tuberculosis Research Network in September of 2018 and published in March of the following year.[17] The document included recommendations for the diagnosis, management, and follow-up of drug-susceptible and drug-resistant cases, pointing out innovations in case management within the *Redes de Atenção à Saúde* (RAS, Health Care Networks).

Measures taken to control multidrug-resistant tuberculosis

Chart 1 presents the documents that were analyzed and that guide MDR-TB care in Brazil by title, year of publication, institution responsible for its development and/or dissemination, and major contributions. The data from the documents were selected and grouped by category as follows: MDR-TB case definition, diagnostic criteria, treatment, use of DOT; mechanisms of social protection for patients; data tools; and organization of care.

Up until 2004 in Brazil, MDR-TB cases were defined as those in which patients experienced bacteriological treatment failure, as mentioned above. In 2007, with the publication of the Guide for Epidemiological Surveillance of Multidrug-Resistant Tuberculosis,[11] MDR-TB case definition was qualified by the requirement of drug susceptibility test results showing resistance to rifampin and isoniazid and to at least one more component of regimens I or III, regardless of the treatment regimen being used. Another possible definition for MDR-TB in the guide was the occurrence of resistance to rifampin and isoniazid accompanied by confirmed bacteriological

Chart 1. Identification of the publications that guide multidrug-resistant tuberculosis care in Brazil by title, year of publication, institution responsible for its development and/or dissemination, and major contributions. Ribeirão Preto, Brazil, 2019.

Document (year of publication)	Institution responsible for its development/ dissemination	Major contributions
Second Brazilian Consensus on Tuberculosis: Brazilian Guidelines on Tuberculosis (2004)[10]	Brazilian Thoracic Association JBP	Regulates the measures proposed by the First Brazilian Consensus on TB: DOT as a recommended strategy to improve treatment adherence, reduce treatment abandonment rates, increase cure rates, and intervene in disease transmission and in the risk of developing drug resistance. The components of the DOTS strategy are perceived by the Brazilian National Ministry of Health as viable for implementation in the different regions of Brazil, as long as local characteristics are taken into account.
Guide for Epidemiological Surveillance of Multidrug-Resistant Tuberculosis (2007)[11]	Brazilian National Ministry of Health. Professor Hélio Fraga Referral Center	Provides specific information about MDR-TB, such as concepts, diagnosis management, treatment, and case follow-up, as well as prevention and required human resources. Of note are the specificities of the professional categories and the management of the databases, which are reported in an organized and clear manner in the document.
Technical Note on Changes in the Treatment of Tuberculosis in Brazil for Adults and Adolescents (2009)[12]	Brazilian National Ministry of Health. Brazilian National Tuberculosis Control Program	Disseminates changes in the TB treatment system. The change in the treatment regimens creates a "basic regimen" for drug-susceptible cases and alters the definition of MDR-TB in Brazil from then on, in line with the WHO recommendations.
Third Brazilian Thoracic Association Guidelines on Tuberculosis (2009)[13]	Brazilian Thoracic Association JBP	Clearly show the need for health care administrators, health care workers, members of society, and organized segments of society to work together. Address MDR-TB, describing a standard treatment regimen, new drugs, surgical indications, and case reporting.
Brazilian National Guidelines for the Control of Tuberculosis (2011)[14]	Brazilian National Ministry of Health. Brazilian National Tuberculosis Control Program	Address MDR-TB in one of their chapters, offering recommendations regarding practices for case management and reporting and the duties of various levels of MDR-TB care.
Technical Memo no. 9 (2014)[15]	Brazilian National Ministry of Health. Brazilian National Tuberculosis Control Program	Reports the news of RMTs for TB and the identification of resistance to rifampin, as well as addresses the status of the implementation of the RMT network in Brazil.
Technical Memo no. 8 (2016)[16]	Brazilian National Ministry of Health. Brazilian National Tuberculosis Control Program	Disseminates new recommendations for the treatment of MDR-TB and RR-TB. Recommends that RR-TB be treated as MDR-TB until AST results become available. Reports changes in the drugs used and in the duration of injectable drug therapy.
Brazilian National Guidelines for the Control of Tuberculosis (2018)[17]	Brazilian National Ministry of Health. Brazilian National Tuberculosis Control Program	Address MDR-TB in one of their chapters, offering recommendations regarding practices for case management and reporting and regarding the duties of the various levels of MDR-TB care. In other chapters, these guidelines address contexts within which multidrug-resistance is embedded, such as within the Health Care Networks.

TB: tuberculosis; DOT: directly observed treatment; DOTS: directly observed treatment, short-course; MDR-TB: multidrug-resistant tuberculosis; WHO: World Health Organization; RMT: rapid molecular test(ing); RR-TB: rifampin-resistant tuberculosis; and AST: antimicrobial susceptibility testing.

treatment failure with regimen III. Already at that time, the WHO defined MDR-TB as a disease caused by a bacillus that was resistant only to rifampin and isoniazid. This criterion was adopted in Brazil in 2011 and is still used today.[14,17]

More recently, with the advent of RMTs, especially Xpert MTB/RIF, another definition has been gaining increasing prominence in the international literature: that of RR-TB cases. The use of RMTs was incorporated into Technical Memo no. 9,[15] and its importance for the diagnosis of RR-TB cases and for control of the disease in Brazil was reaffirmed in the 2018 Brazilian National Guidelines for the Control of Tuberculosis.[17] The 2018 guidelines also incorporated the concept of "pre-XDR-TB", which is used to describe cases in which, in addition to resistance to rifampin and isoniazid, there is resistance to a fluoroquinolone or a second-line injectable drug.[17]

The diagnostic criterion is closely associated with case definition and with laboratory confirmation of

drug resistance via sputum culture and antimicrobial susceptibility testing (AST). The first important recommendation in this regard was found in the 2009 Technical Note,[12] in which it was recommended that culture and AST be performed in all cases of retreatment; up until then, the use of these tests depended on the clinical and epidemiological status of the patient under investigation and the available laboratory resources.[13]

In 2014, Technical Memo no. 9[15] recommended the use of an RMT in the following cases: screening for rifampin resistance; early identification of treatment failure in patients using the basic regimen; and diagnosis of new cases in the general population and in vulnerable populations. However, the use of RMTs was not recommended for treatment follow-up or diagnosis in cases of retreatment, because an RMT detects live and dead bacilli.

In the 2018 Brazilian National Guidelines for the Control of Tuberculosis,[17] an algorithm for the diagnosis of cases in settings where RMTs are available and in settings where RMTs are unavailable was provided, as were the steps for the diagnostic investigation and management of cases with conflicting test results. The need for performing sputum culture and AST was reaffirmed, and the need for assessment of social and clinical risks (clinical course of the case, previous treatment, and bacteriological curve) by specialists at tertiary referral centers in order for a treatment regimen to be selected was also highlighted. In addition, the process of validating cases that are reported to SITE-TB, through consideration of outside specialist opinion, was described.[17]

With regard to the treatment of MDR-TB, Brazil chose to standardize the drug regimens because of laboratory difficulties, although the evidence points to better results when the treatment regimen is individualized on the basis of AST results,[30] and has exercised this choice since then.[5,11] The first standard regimens were the result of a multicenter study conducted in the 1990s and validated nationwide in 2000.[20]

From then on, some changes, mainly related to the use of injectable drugs of choice and their frequency of administration, were made to the regimens. Up until 2016, the recommended frequency of administration of injectable drugs was five times per week for 2 months, then three times per week until treatment month 12.[10] In 2016, this frequency was changed to three times per week for 8 months. However, optimal treatment prescription was dependent on the clinical and bacteriological status of each patient receiving pharmacological therapy.

With regard to injectable drugs, the Second Brazilian Consensus on Tuberculosis and the Guide for Epidemiological Surveillance of Multidrug-Resistant Tuberculosis recommended a regimen containing amikacin as the regimen of choice.[10,11] However, in 2009, when the treatment regimens as a whole were changed, the use of injectable streptomycin began to be recommended, and amikacin was reserved for use in cases in which it was not possible to use streptomycin.[12-14] In 2016,[16] the use of injectable capreomycin was standardized for the first time, on the basis of the WHO recommendations, literature review, and approval by the PNCT. In addition, the use of ethionamide began to be recommended in cases of confirmed resistance to ethambutol and adjustment in the dose of levofloxacin, as recommended by the WHO.[16] These changes were reaffirmed in 2018[18] and included the addition of clofazimine to the treatment regimens, which is supported by recent studies.[25,31]

It is of note that the 2007 Guide for Epidemiological Surveillance of MDR-TB[11] presented the treatment options in a much more complete way than the documents that had been published up until then, providing a classification and division of antituberculosis drugs into pharmacological groups and a system for choosing the amount and diversity of drugs, as well as information about the properties of each drug and its major side effects. These aspects were maintained in the 2011 and 2018 Brazilian National Guidelines for the Control of Tuberculosis,[14,17] and the latter expanded the treatment options for RR-TB cases in settings where RMTs are available.[17]

It is recommended that tuberculosis therapy be administered as an outpatient regimen under supervision via DOT. All documents, to a greater or lesser extent, refer to the need to ensure treatment adherence; however, up until 2018,[17] the characteristics of patients with drug resistance had not been addressed. In 2004, the Second Brazilian Consensus on Tuberculosis[10] already acknowledges the need for treatment supervision, at that time named supervised treatment, priority being given to patients with MDR-TB. In 2011, the chapter on DOT had five pages, with no specific recommendations for cases of MDR-TB.[14] Up until then, there had been a significant gap in the organization of care because of the profile of the patients with greater clinical severity and greater social deprivation, whose management required greater efforts on the part of the teams.[32]

In this regard, the recommendations provided by the 2018 Brazilian National Guidelines for the Control of Tuberculosis[17] made a great leap, approaching those provided by the End TB strategy, namely: DOT throughout treatment, ideally five times per week or at least three times per week; possibility of carrying out DOT in various places; and the need to make choices in partnership with patients and their families "in a welcoming and supportive way".[17] In addition, the need was highlighted for DOT to be carried out in partnership with primary care, which, in turn, would have the responsibility of monitoring treatment adherence, adverse effects, and complications on a permanent basis. The possibility of referring patients and patient information to a tertiary referral center was acknowledged, although the forms of referral were not regulated.[17]

Another important aspect that has been discussed in other contexts in order to improve treatment

adherence is family involvement and support, which was recommended in 2018, but no great details about how to put that into practice were provided.[17] Studies conducted in Peru and Africa have demonstrated the importance of a community supporter, who may be a family member or someone who has been cured of MDR-TB, for strengthening treatment adherence and fighting the social stigma of the disease.[33,34]

With regard to mechanisms of social protection for patients, three of the documents analyzed indicated the need for provision of incentives, such as public transportation passes and baskets of food items, in order to increase treatment adherence.[11,14,17] In none of the documents analyzed was it possible to find the regulation of financial resources specifically intended for the provision of incentives at health care facilities.

Advances toward providing a holistic approach to patients can be observed in the 2018 Brazilian National Guidelines for the Control of Tuberculosis,[17] which address actions and partnerships to fight the social determinants of health that affect the various stages of disease pathogenesis. The challenges of overcoming poverty and promoting social development are presented, and intersectoral action is reported as an overcoming strategy.[17] The document addresses the continuing care benefit and the special social protection mechanisms to which patients with tuberculosis may resort to depending on their needs, as well as the possibilities of access to Social Security, sickness benefit, and disability retirement, all of which are conditional on previous contributions by the beneficiary. In addition, the document presents the main goals of the joint efforts of the NMH and the Brazilian Ministry of Social Development regarding intersectoral actions, including the establishment of flows between health care facilities and social care centers; assurance of food and nutritional security; integrated care plans (health and social care) for patients and their families; search for institutional care alternatives during the treatment of homeless patients; "promotion of health education activities at social care centers and dissemination of social care mechanisms at health care facilities"; and assurance of care for people who do not have an identification document, at health care facilities.[17]

With regard to information flow, it was possible to observe the evolution of the dedicated database over time through the analysis of the documents mentioned above. In the 2007 document,[18] it is possible to have a preliminary idea of the structure of the database that had been developed through a partnership between the CRPHF and Management Sciences for Health. The document presented the Internet computerized MDR-TB surveillance database, access to which was restricted to registered professionals with diverse profiles; the use of the database allowed one to follow patients undergoing treatment, seek information, and rationalize the use of medications. In addition, the document provided a flowchart of the information flow within the database and addressed the need for case validation by a referral center.[18]

Since 2013, the database called SITE-TB, which is a modified version of the MDR-TB surveillance database, has allowed case reporting, case follow-up, and case outcome reporting, classifying the different types of DR-TB.[8] In addition to being used for the reporting of cases of drug resistance, the database has been used for managing information about special treatments and nontuberculous mycobacteria, as well as for medication management, which allows dispensing, ordering, receipt, transfers, and inventory control.[35]

SITE-TB shows significant similarities to other databases used in the follow-up of cases of MDR-TB, because it allows communication among the various professionals involved in care. However, in parallel to its use, there is a need to report cases to other databases, none of which share data, and this results in data redundancy and rework for the professionals involved.[36] Another important limitation of SITE-TB is that it does not allow access by primary health care professionals; its information is intended solely for secondary and tertiary levels of health care.

Technical Memo no. 9[15] offers recommendations on the timing of case reporting to SITE-TB—when drug resistance is confirmed—which should occur concomitantly with case outcome reporting to the Brazilian Case Registry Database. It highlights the importance of updating the database to prevent drug shortages.[15] Technical Memo no. 8 also supports these recommendations.[16] However, it is in the 2018 Brazilian National Guidelines for the Control of Tuberculosis[17] that SITE-TB gains prominence with a detailed description of its functionality; case reporting and validation flow; definition of admission types and predicted outcomes; classification of cases entered in the database by drug resistance pattern; treatment follow-up and post-cure follow up; and medication management and planning.[17]

Given that patients with MDR-TB move through various levels of care, regulating how care should be organized, acknowledging its flows and counterflows, is extremely important for case management and for obtaining favorable results. The role of health care facilities was first defined in 2007.[11] Up until then, more complex cases were referred to referral centers, usually state ones.[19]

The 2007 Guide for Epidemiological Surveillance of MDR-TB[11] describes in detail the activities that should be carried out at referral health care centers, the role and duties of the various occupational categories (both at the primary and specialist care level), and the role of the PNCT's national, state, and municipal councils. It is recommended that cases be followed by a multidisciplinary team, and tertiary referral centers are responsible for the therapeutic management of all cases of drug resistance. Although emphasis is placed on primary care as the initial support network and on the importance of a structured referral and counter-referral network, there are no details regarding the duties at this level of care.[11]

The 2011 Brazilian National Guidelines for the Control of Tuberculosis[14] made it clearer which cases should be followed at each specific level of care in the chapter "Structure of Care for the Person with Tuberculosis", in which cases of drug resistance are included. Among the duties in primary care was patient referral to referral centers when there was drug resistance, treatment failure, comorbidities, important adverse effects, or difficulty in making a diagnosis: "receive and follow patients treated at referral centers and referred back to primary care, carrying out supervised treatment and investigating contacts (counter-referral)". As for communication among the various facilities, the need to record DOT on a "supervised treatment card" was mentioned; however, no model or definition of such a card was provided. The 2011 guidelines[14] also addressed hospital units and the laboratory network.

The 2018 Brazilian National Guidelines for the Control of Tuberculosis[17] went a step further regarding the organization of care, because they incorporated the 2011 RAS, contextualized tuberculosis care, and defined the role of long-stay hospitals.[37] However, in a practical sense, they did not present significant changes in the definition of flows and counterflows in the Brazilian Unified Health Care System or provide mechanisms for promoting the integration of the health care system in terms of MDR-TB care. In addition, they did not clearly identify the tertiary referral centers, where they were located, or what was their catchment area.[17] That information was not found in any of the documents analyzed.

Another significant gap in MDR-TB care in Brazil is the lack of formal mechanisms of communication among levels of care, given that the aforementioned "supervised treatment card" was not found and SITE-TB does not allow access by primary health care professionals. Therefore, although the 2018 Brazilian National Guidelines for the Control of Tuberculosis[17] went a step further in that they incorporated the RAS principles, in practice, the tools for care coordination among the various health care facilities involved were not well established, leading to fragmentation of care.

FINAL CONSIDERATIONS

The present study summarized the recommended actions and the efforts made in recent decades in Brazil for the effective control of MDR-TB. We noted a closer approximation to the WHO recommendations and definitions, which is a reflection of the change in case definition and adjustments in the standard regimens, as well as of the incorporation of new diagnostic technologies that allowed the identification of RR-TB.

The documents went a step further in that they acknowledge the need for social protection for patients with MDR-TB. However, they still lack a concrete proposal for the operationalization of social protection within the Social Security System in Brazil, with equitable measures to treat such a socially diverse population. From the same perspective, the fact that providing incentives has the potential to improve treatment adherence is acknowledged; however, the financial resources to be allocated for that purpose are not defined.

The necessary skills for the various professionals that are charged with treating MDR-TB at the various levels of care were defined, as were the measures that should be taken at each such level. Such organization needs to be presented in official publications. We believe that this is well established in the work routine of health care teams, given that MDR-TB patients are treated at referral centers. In this regard, the organization of care is moving toward the establishment of tools for communication among the various health care facilities involved in the care of these patients.

AUTHOR CONTRIBUTIONS

JGAB conceived the proposal, guided data collection, and assisted in the organization of results, discussion of findings, and writing of the manuscript. JMG contributed to the writing of the research proposal, data collection, organization of results, and writing of the manuscript. VRB, ARN, and MPD contributed to the improvement of the methodology, discussion of results, and writing and revision of the final version of the manuscript. ACSM contributed to the organization and discussion of results, as well as to the writing of the manuscript. IZR and NSM assisted in data collection, literature review, updating of reverences, and writing of the manuscript. PFP guided the proposal, obtained institutional funding, and contributed to data collection, organization of results, and discussion and revision of the final version of the manuscript.

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