

III Brazilian Thoracic Association Guidelines on Tuberculosis

III Diretrizes para Tuberculose da Sociedade
Brasileira de Pneumologia e Tisiologia

BTA Committee on Tuberculosis¹, BTA Guidelines on Tuberculosis Work Group²

Abstract

New scientific articles about tuberculosis (TB) are published daily worldwide. However, it is difficult for health care workers, overloaded with work, to stay abreast of the latest research findings and to discern which information can and should be used in their daily practice on assisting TB patients. The purpose of the III Brazilian Thoracic Association (BTA) Guidelines on TB is to critically review the most recent national and international scientific information on TB, presenting an updated text with the most current and useful tools against TB to health care workers in our country. The III BTA Guidelines on TB have been developed by the BTA Committee on TB and the TB Work Group, based on the text of the II BTA Guidelines on TB (2004). We reviewed the following databases: LILACS (SciELO) and PubMed (Medline). The level of evidence of the cited articles was determined, and 24 recommendations on TB have been evaluated, discussed by all of the members of the BTA Committee on TB and of the TB Work Group, and highlighted. The first version of the present Guidelines was posted on the BTA website and was available for public consultation for three weeks. Comments and critiques were evaluated. The level of scientific evidence of each reference was evaluated before its acceptance for use in the final text.

Keywords: Tuberculosis; Mycobacterium infections; Diagnosis; Tuberculosis, multidrug-resistant.

Resumo

Diariamente novos artigos científicos sobre tuberculose (TB) são publicados em todo mundo. No entanto, é difícil para o profissional sobrecarregado na rotina de trabalho acompanhar a literatura e discernir o que pode e deve ser aplicado na prática diária juntos aos pacientes com TB. A proposta das “III Diretrizes para TB da Sociedade Brasileira de Pneumologia e Tisiologia (SBPT)” é revisar de forma crítica o que existe de mais recente na literatura científica nacional e internacional sobre TB e apresentar aos profissionais da área de saúde as ferramentas mais atuais e úteis para o enfrentamento da TB no nosso país. As atuais “III Diretrizes para TB da SBPT” foram desenvolvidas pela Comissão de TB da SBPT e pelo Grupo de Trabalho para TB a partir do texto das “II Diretrizes para TB da SBPT” (2004). As bases de dados consultadas foram LILACS (SciELO) e PubMed (Medline). Os artigos citados foram avaliados para determinação do nível de evidência científica, e 24 recomendações sobre TB foram avaliadas, discutidas por todo grupo e colocadas em destaque. A primeira versão das “III Diretrizes para TB da SBPT” foi colocada no *website* da SBPT para consulta pública durante três semanas, e as sugestões, críticas e o nível de evidência da referência científica que as embasavam foram avaliados e discutidos antes de serem incorporadas ou não ao texto final.

Descritores: Tuberculose; Infecções por Mycobacterium; Diagnóstico; Tuberculose resistente a múltiplos medicamentos.

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Introduction

The United Nations Millennium Development Goals for Tuberculosis (TB) are aimed at effecting a 50% reduction in the rates of TB incidence and mortality by 2015. Brazil continues to be one of the 22 countries that, together, account for 90% of all TB cases worldwide. However, as of 2007, there had been a 26% decrease in incidence and a 32% decrease in mortality in our country. This decrease has become accentuated since the implementation of the DOTS strategy in 1999. The incidence rate of TB in Brazil during this period is presented in Figure 1.

The incidence rate of TB by region ranged from approximately 30 cases/100,000 population in the southern and central-west regions to approximately 50 cases/100,000 population in the northern, northeastern, and southeastern regions.

According to the Brazilian NMH, the highest incidence rates are among males and in the 45-59 year age bracket. In 6.2% of the cases, TB/HIV co-infection was found (although HIV testing is requested in less than half of all TB cases). The states of Rio Grande do Sul, Santa Catarina, and São Paulo showed the highest percentages, whereas the states of Acre and Roraima showed the lowest percentages. In 2006, the rates of cure and noncompliance were, respectively, 73% and 9% for new cases and 57% and 14% for HIV-positive cases. In addition, there was a 31% decrease in the mortality rate per 100,000 population from 1990 to 2006. According to data from the NMH, in 2006, the mortality rate in the northeastern region was the

highest, followed by that found in the south-eastern region.

The purpose of the III Brazilian Thoracic Association (BTA) Guidelines on TB is to critically review the most recent national and international scientific information on TB, presenting an updated text with the most current and useful tools against TB to health care workers in our country.

In addition to the scientific aspects addressed in these Guidelines, it is clear, for the BTA, that a joint effort including the civil society and its organized segments, as well as health care administrators and health care workers, is necessary. Only the coordinated effort of all of the actors involved in this fight will make it possible to achieve the targets and the six goals of the Stop TB Partnership Second Global Plan to Stop TB (2006-2025): expanding and improving the DOTS strategy; addressing TB/HIV co-infection and multidrug resistant TB, as well as other challenges; strengthening health care systems; engaging all healthcare providers; empowering TB patients and communities; and promoting research.

Methods

The III BTA Guidelines on TB have been developed by the BTA Committee on TB and the TB Work Group, based on the text of the II BTA Guidelines on TB (2004). A review of the recent literature, including articles written in Portuguese, as well as articles in English, was conducted based on searches of the following databases: LILACS (SciELO) and PubMed

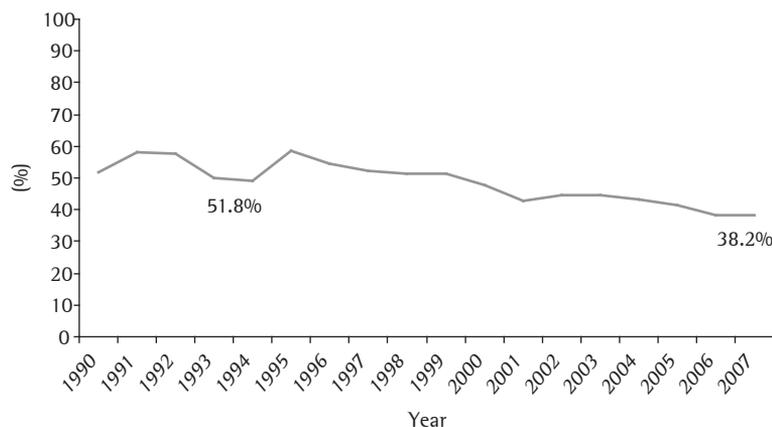


Figure 1 – Historical study of the incidence rate of TB by year, Brazil, 1990–2007.

(Medline). The major recommendations under each topic were discussed and highlighted. The cited articles are accompanied by their level of evidence (in square brackets), as determined by the editors of the topics, in accordance with the Oxford Centre for Evidence-Based Medicine criteria (<http://www.cebm.net>). Cited articles from manuals and textbooks, as well as from guidelines established by organizations, foundations, or scientific societies, are not accompanied by their level of evidence.

The first version of the present text was written between February and May of 2009 and posted on the BTA website in May of 2009 for public comment. On June 19 and 20, the members of the BTA Committee on TB and of the TB Work Group, as well as the colleagues who sent suggestions during the public comment period and expressed their desire to participate, met in order to review the final text, which was then sent to the editor of the Brazilian Journal of Pulmonology in July of 2009.

The abbreviations and acronyms used in the III BTA Guidelines on TB are presented in Chart 1, the definitions are presented in Chart 2, and the recommendations are presented in Chart 3.

Epidemiology of TB

The three essential components of epidemiology are the frequency of occurrence of a disease, its distribution, and its determining factors. In order to monitor the frequency of occurrence of a disease, there must be an epidemiological surveillance system that makes it possible to detect the occurrence of the event quite accurately. In Brazil, this function is performed by the *Sistema Nacional de Agravos de Notificação* (SINAN, National Case Registry Database), which monitors contagious infectious diseases, and by the Mortality Database, which has information on overall and specific mortality. Although these databases have been under implementation for years, they still need to be improved. The search for determining social factors of the disease requires research in areas such as economics, politics, sociology, anthropology, etc. A comprehensive theoretical starting point will encompass aspects of the superstructure of society and aspects of its infrastructure.

In conclusion, the different levels of research required for the epidemiology of TB are listed below:

Chart 1 – Abbreviations and acronyms.

ADA	adenosine deaminase	NMH	National Ministry of Health
AFB	acid-fast bacilli	NRTIs	nucleoside reverse transcriptase inhibitors
ALT	alanine aminotransferase	NTCP	National Tuberculosis Control Program
ARV	antiretroviral	NTM	nontuberculous mycobacterium
AST	aspartate aminotransferase	O	ofloxacin
ATS	American Thoracic Society	PAL	Practical Approach to Lung Health
CNS	central nervous system	PAS	para-aminosalicylic acid
DOTS	Directly Observed Therapy, Short-course	PCR	polymerase chain reaction
E	ethambutol	PPD	purified protein derivative
Et	ethionamide	R	rifampin
FDA	Food and Drug Administration	S	streptomycin
FDC	fixed-dose combination	SRD	symptomatic respiratory disease
GL	gastric lavage	T	terizidone
H	isoniazid	TAC	Technical Assessment Committee
HEPA	high-efficiency particulate air	TB	tuberculosis
IGRA	Interferon-Gamma Release Assay	TST	tuberculin skin test
IUATLD	International Union Against Tuberculosis and Lung Diseases	ULN	upper limit of normality
IRIS	immune reconstitution syndrome	WHO	World Health Organization
LTB	latent tuberculosis	XDR-TB	extensively drug-resistant tuberculosis
MDR-TB	multidrug-resistant tuberculosis	Z	pyrazinamide
Mtb	<i>Mycobacterium tuberculosis</i>		
NAA	nucleic acid amplification		

Chart 2 – Definitions

Noncompliance with treatment	<ul style="list-style-type: none"> • Discontinuation of treatment for TB for 30 days or more after the predicted date of return (self-administered treatment) or 30 days after the last drug intake (supervised treatment).
High-risk environment	<ul style="list-style-type: none"> • Places where the risk of Mtb infection, from patient to healthy individuals, from patient to patient, or from patient to health care workers, is high.
Active surveillance	<ul style="list-style-type: none"> • Surveillance of cases of pulmonary TB (e.g., in the community, in high-risk groups, etc.) in individuals with SRD who did not spontaneously seek medical attention or who (spontaneously) sought medical attention for a reason other than cough.
Passive surveillance	<ul style="list-style-type: none"> • Investigation of TB in individuals with SRD who spontaneously sought medical attention due to cough.
Case of recurrence	<ul style="list-style-type: none"> • A case in which the patient is currently diagnosed with bacteriologically positive TB (sputum smear microscopy or culture) and has a history of TB cured with anti-TB drugs.
New or treatment-naïve case	<ul style="list-style-type: none"> • A case in which the patient has never received treatment for TB for 1 month or more.
Contact with TB	<ul style="list-style-type: none"> • Exposure to AFB-positive cases for at least 200 h or exposure to AFB-negative cases with positive culture for at least 400 h, and only exposure in enclosed spaces is valued.
Diagnosis of TB	<ul style="list-style-type: none"> • Positive culture for Mtb.
Presumptive diagnosis of TB	<ul style="list-style-type: none"> • Presence of two AFB-positive smears or one AFB-positive smear accompanied by X-ray findings suggestive of TB or histopathology revealing granuloma, with or without caseous necrosis, in clinically suspected cases.
Booster effect	<ul style="list-style-type: none"> • TST with an induration ≥ 10 mm after the TST performed 1-2 weeks prior yielded an induration ≥ 6 mm.
Retreatment due to noncompliance	<ul style="list-style-type: none"> • A case in which a bacteriologically positive patient resumes the treatment after noncompliance.
Symptomatic respiratory disease	<ul style="list-style-type: none"> • Presence of cough or dyspnea or chest pain, accompanied or not by expectoration or hemoptysis or wheezing. In the investigation of pulmonary TB, cases of SRD will be defined as those in which individuals have cough.
Immune reconstitution syndrome	<ul style="list-style-type: none"> • Pronounced inflammatory reaction in patients with TB/HIV co-infection occurring after the initiation of highly active ARV therapy. It presents fever, weight loss, and lymph node enlargement, as well as pulmonary consolidation and pleural effusion. Histologically, there is granulomatous reaction with or without caseation. It can occur in HIV-negative patients after the initiation of treatment for TB.
Multidrug-resistant TB	<ul style="list-style-type: none"> • Mtb resistant to RH.
Extensively-drug-resistant TB or XDR-TB	<ul style="list-style-type: none"> • Mtb resistant to RH and to one fluoroquinolone, plus resistant to one of three second-line injectable drugs (amikacin, kanamycin, or capreomycin).
Polydrug-resistant TB	<ul style="list-style-type: none"> • TB resistant to R or to H + another drug.
Negative smear microscopy TB	<ul style="list-style-type: none"> • Presence of at least two AFB-negative sputum samples (including one sample collected in the morning); X-ray findings consistent with TB or no clinical response to treatment with broad-spectrum antimicrobial agents (Note: fluoroquinolones should not be used since they have activity against the Mtb complex and can cause temporary improvement in TB patients); satisfactory response to anti-TB treatment.
Tuberculin skin test conversion	<ul style="list-style-type: none"> • An induration increase ≥ 10 mm between TSTs performed 2 weeks to 2 years apart.

Chart 3 – Recommendations of the III BTA Guidelines on TB.

Surveillance of cases of active TB

- 1) For the purpose of passive or active surveillance of cases of pulmonary TB, consider individuals with SRD as those who have had cough for 2 weeks or more.
- 2) For the purpose of passive surveillance of TB, request chest X-ray and direct sputum smear examination for AFB.

Diagnosis of active TB

- 3) Patients suspected of having pulmonary TB should have at least two sputum samples collected for mycobacteriological testing, and, when possible, at least one sample should be collected in the morning.
- 4) Individuals with SRD presenting chest X-ray findings suggestive of TB should have at least one sputum sample submitted to culture for TB and susceptibility testing (in addition to smear examination for AFB) whenever possible.
- 5) Patients suspected of having TB based on chest X-ray findings and presenting no spontaneous expectoration should be submitted to sputum induction.

New techniques for the diagnosis of TB

- 6) There are currently no new methods for the diagnosis of TB validated for routine use.

Latent Mtb infection or LTB

- 7) Chest X-ray and the TST should be performed in all individuals who have been in contact with an adult with active pulmonary TB, regardless of their age.
- 8) Previous BCG vaccination should be taken into account in the interpretation of TST results within the first 2 years after vaccine administration.
- 9) The treatment of latent Mtb infection is indicated for individuals without active TB who belong to high-risk groups and have positive TST results.

Treatment of active TB

- 10) The basic regimen for the treatment of TB (individuals aged 10 years or older) will include four drugs in the first 2 months and two drugs in the following 4 months (2RHEZ/4RH).
- 11) The change in the treatment regimen proposed by the NTCP (2RHEZ/4RH) should have its effectiveness evaluated by studies conducted in referral centers.
- 12) All of the regimens for the treatment of TB should be administered in a supervised manner.

TB in special situations and comorbidities (including HIV)

- 13) HIV testing should be offered to all TB patients.
- 14) The TST should be requested in all HIV-positive patients who have not been diagnosed with active TB.
- 15) In severely immunocompromised patients suspected of having TB, treatment should be instituted while waiting for the laboratory test results.
- 16) In all patients with TB/HIV co-infection, sputum culture and susceptibility testing should be performed.

New drugs for the treatment of TB

- 17) There is no scientific evidence to justify the inclusion of new drugs in the current treatment regimen.

Surgical treatment of TB

- 18) The selection criteria for resection in pulmonary TB are still controversial, and the studies published are not definitive with regard to the benefits of resection.

Childhood TB

- 19) The diagnosis of TB in children, given the paucibacillary characteristic of this disease, should be based on epidemiological, clinical, and radiological criteria.
- 20) Treatment for TB should be indicated for all children diagnosed with active pulmonary TB based on the scoring system (≥ 30 points).
- 21) Chemoprophylaxis is indicated in neonates born to mothers with pulmonary TB who present AFB-positive sputum smears and in children with LTB.
- 22) The addition of corticosteroids to the anti-TB regimen is indicated in tuberculous meningoencephalitis.

TB and biosafety

- 23) Biosafety measures should be adopted in high-risk environments for TB transmission.

TB and smoking

- 24) Smoking cessation strategies and programs should be incorporated in the treatment of TB patients.

- Aspects related to the host, such as immunogenetic profile, nutrition, new vaccines, disease transmission dynamics, and risk of infection.
- Clinical aspects, such as treatment regimens of shorter duration and new diagnostic kits offering an appropriate cost-benefit relationship.
- Epidemiological aspects and aspects related to health care facilities, with analyses of the structure, the process, and the results; indicators of use of the structure; indicators of the processes; adherence to treatment; number of patients treated; accessibility; variety of services; continuity; level of use; longitudinality; integration; coordination; and assessment of the effectiveness of the primary care attributes. In addition, operational studies that make it possible to use the knowledge produced and to analyze the factors that facilitate the application of such knowledge or make it unfeasible are necessary, as are studies on the cultural barriers to putting public health programs into practice, laboratory studies, training and standardization programs for laboratory technicians, TB control programs in hospitals, studies on the epidemiology of TB among migrants, and the monitoring of multidrug-resistant and super-resistant strains.
- Aspects of the geographical and epidemiological approach to TB, with geoprocessing and geostatistical techniques, with the purpose of estimating high-risk areas, identifying the distribution of the population groups and the migration flows, in addition to providing strategic information to administrators of health care facilities. Further studies on the sensitivity, specificity, representativeness, opportunity, predictive value, simplicity, flexibility, and acceptability of the epidemiological surveillance system are needed.

Surveillance of cases of active pulmonary TB in adults

Although cases of pulmonary TB usually present as cases of SRD, pulmonary TB accounts for only 1.4–3.0% of the total number of cases of SRD treated at health care facilities, and, therefore, the WHO suggests that the approach

to cases of SRD be systematized and include the investigation of other diseases, such as acute respiratory infection, asthma, and COPD, in addition to TB.^(1[2A]) This strategy, known as PAL, aims to strengthen health care systems by linking TB control activities and health care facilities.⁽²⁾ For the purpose of surveillance of cases of pulmonary TB, cases of SRD will be defined as those in which individuals have cough, since cough is the most common symptom of pulmonary TB. Figure 2 presents a proposed algorithm for implementing the PAL strategy.

Delayed identification of cases of pulmonary TB occurs due to inadequate assessment of cases of SRD or to a delay in seeking medical attention. Studies conducted in Brazil have demonstrated a 7-week interval between the first visit and the initiation of treatment and a 10- to 12-week interval between the onset of symptoms and the initiation of treatment.^{(3[2C]),(4[2C]),(5[3A])}

The principal strategies for surveillance TB cases are passive surveillance and active surveillance. The Brazilian NMH recommends that two to three spontaneous sputum samples be collected from patients who have had respiratory symptoms, i.e. cough, for 3 or more weeks for direct smear examination for AFB.⁽⁶⁾ However, studies conducted in Brazil and in India have shown that the reduction in cough duration to 2 weeks increases the number of TB cases at the cost of only a slight growth in the health care system workload.^{(7[2C]),(8[3B])}

Only half of the patients with pulmonary TB are smear-positive for AFB on direct examination, and up to 30% of the patients cannot produce sputum spontaneously in the initial phases of the disease. Therefore, in the initial approach to cases of SRD, chest X-ray has a significant impact on the early detection of pulmonary TB.^{(9),(10[3A])} In addition, in most cases of SRD, individuals have a respiratory disease other than pulmonary TB, and, consequently, chest X-ray plays a fundamental role in the assessment of such individuals.^{(1[2A]),(7[2C])}

Active surveillance is a multidisciplinary activity with the purpose of diagnosing TB early, especially in groups at a higher risk of developing the disease, such as the following^{(9),(11[2A]),(12[2C]),(13[2C]),(14[2C])}:

- communities with a high prevalence of TB
- individuals who have been in contact with a case of pulmonary TB

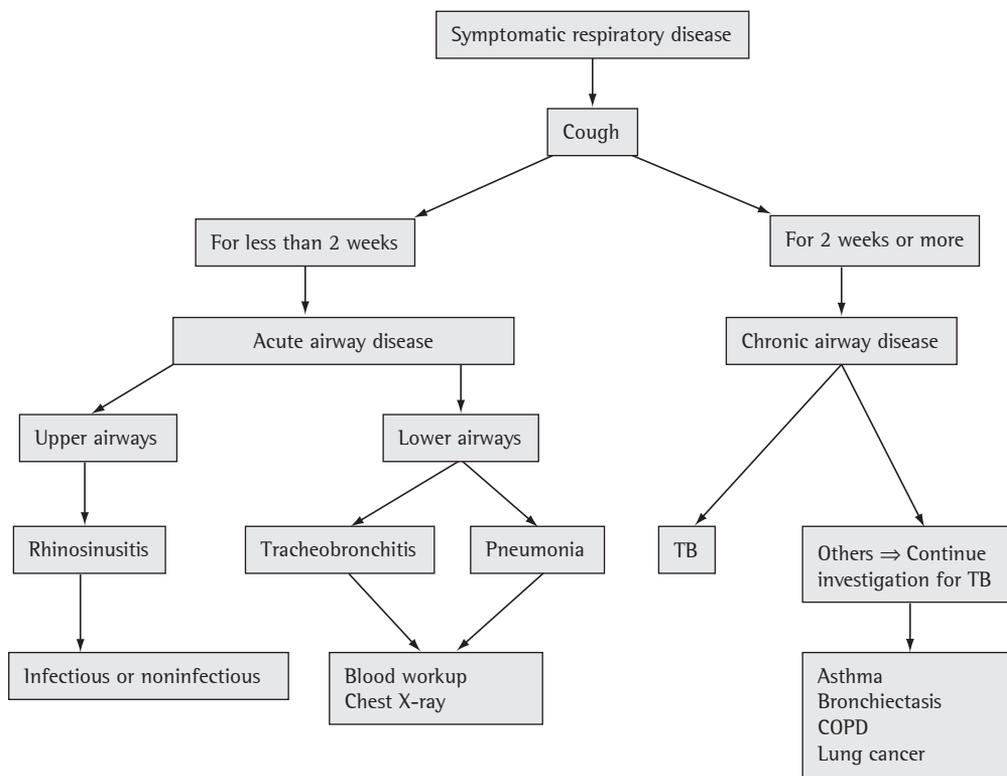


Figure 2 - Proposed PAL algorithm for individuals with cough. Adapted from the World Health Organization Practical Approach to Lung Health.⁽²⁾

- HIV-positive individuals or individuals with other immunosuppressive conditions
- individuals residing in shelters or nursing homes
- prison inmates and health care workers

The first tool used in active surveillance is the identification of cases of SRD by actively asking individuals about the presence of cough for at least 2 weeks.^{(9), (11[2A])}

Active surveillance through sputum smear examination for AFB in cases of SRD is less effective than are passive surveillance and TB education activities, both at health care facilities and in the community.^{(7[2C]), (15[2C]), (16[1B]), (17[3A]), (18[1B])} However, in regions with a high prevalence of TB and a functionally deficient health care system, active surveillance at health care facilities and in the community plays a complementary role to passive surveillance since it contributes to the early diagnosis of infectious cases, shortening duration of disease transmission. Nevertheless, the cost-effectiveness of this strategy is unknown. In a study conducted in India, 70% of the AFB-positive cases detected via active surveillance knew about their respiratory symp-

toms, and 50% had previously sought medical attention.^(19[2C]) In addition, the likelihood of noncompliance with treatment is greater among the cases detected in the community via active surveillance, and, therefore, this strategy is preferably recommended for areas under coverage of the DOTS strategy.^{(11[2A]), (20[3A]), (21[1B])}

Conversely, active surveillance in populations at increased risk of TB, such as individuals who have been in contact with a case of pulmonary TB, individuals residing in shelters or nursing homes, and prison inmates or health care workers, is the most effective strategy to reduce costs and increase case detection.^{(9), (11[2A])} In those groups, chest X-ray is indicated in cases of SRD in which individuals have had cough for 2 weeks or more or in those in which individuals have a positive TST result during the investigation of latent Mtb infection, regardless of the presence of symptoms. In individuals presenting chest X-ray findings suggestive of TB, examination of respiratory specimens for AFB and mycobacterial culture of respiratory specimens are indicated.^{(6,9), (22[2C])} Due to the high prevalence of TB among prison inmates, the ATS recommends

active surveillance using chest X-ray as the initial method in all such individuals, regardless of the presence of respiratory symptoms.^(9,23)

The surveillance of TB cases among HIV-positive individuals is presented under the topic "TB in special situations and comorbidities (including HIV)".

Diagnosis of TB

Bacteriological diagnosis

The first tests that should be requested are chest X-ray and sputum smear examination for AFB, which has a high positive predictive value (> 95%) in Brazil, but a low sensitivity (40-60%). In Brazil, Ziehl-Neelsen staining is the standard procedure.⁽²⁴⁾ Auramine staining with readings taken using an immunofluorescence microscope is indicated for screening in laboratories that process 30-50 samples/day, reducing the time spent reading negatives. Two spontaneous sputum samples should be collected, one at the time when the individual with SRD seeks medical attention and one in the morning upon waking. In patients who cannot produce sputum spontaneously and present X-ray findings suggestive of TB, sputum induction with hypertonic saline is indicated since it has a diagnostic yield similar to that of bronchoscopy with bronchoalveolar lavage.^(25[2B]) Performing three sputum inductions on different days is more cost-effective for the diagnosis of pulmonary TB than is bronchoscopy.^(26[2B])

Culture makes it possible to identify *Mtb* and perform susceptibility testing, in addition to increasing the diagnostic yield by 20-40%. The most widely recommended solid media are Löwenstein-Jensen and Ogawa-Kudoh. The latter is recommended for use in laboratories that perform procedures of low complexity because it does not require the use of a centrifuge.^(27[3B]) A limitation of solid medium culture is the time required to obtain results (2-8 weeks). Therefore, whenever possible, liquid media should be used in automated nonradiometric systems (results obtained in 10-40 days).

Indications for culture –

- clinically suspected cases of TB with AFB-negative smears
- suspected cases of TB based on X-ray findings

- retreatment cases
- cases of HIV infection
- cases involving vulnerable populations (prison inmates, health care workers, and homeless individuals, as well as individuals residing in shelters, psychiatric hospitals, and nursing homes)
- suspected cases of resistance
- suspected cases of extrapulmonary TB

The identification of species consists in distinguishing *Mtb* complex mycobacteria from NTM.

The indications for susceptibility testing are the same as those for culture. The standardized methods used in Brazil are the proportion method, the resistance ratio method, and the absolute concentration method. Some referral laboratories employ automated systems that use liquid culture (BACTEC MGIT 960 System; Becton Dickinson, Sparks, MD, USA), which reduces the time required to obtain results to 10 days.⁽²⁴⁾

Radiological diagnosis

Primary TB

Although chest X-ray is an important means of diagnosing primary TB, it fails to detect pulmonary changes in up to 15% of cases.^(28[2B]) The principal changes are as follows:

- Parenchymal opacities are usually unifocal and predominate in the right lung, affecting the upper lobes in childhood and the middle and lower lobes in adulthood. Persistent circular opacities measuring up to 3 cm in diameter (tuberculomas) are unusual manifestations (described in up to 10% of cases), more commonly found in the upper lobes, and can be accompanied by calcification of hilar lymph nodes.⁽²⁹⁾
- Lymph node enlargement is observed in most children and in up to 40% of adults. Although it is usually unilateral, it can be bilateral in up to 30% of cases. The most affected regions are the hilar region and the right paratracheal region. It is frequently associated with parenchymal opacities and segmental or lobar atelectasis.
- Atelectasis results from extrinsic airway compression due to lymph node enlargement, being the principal manifestation in

children under 2 years of age. The most affected segments are the anterior segment of the upper lobes and the medial segment of the middle lobe.⁽³⁰⁾

- Miliary pattern consists of small nodular opacities, measuring 1-3 cm in diameter, symmetrically distributed. Asymmetric distribution can occur in up to 15% of cases. It can be accompanied by parenchymal opacities in 40% of cases involving children and less frequently in cases involving adults. Lymph node enlargement is observed in 95% of children and in approximately 10% of adults.^(29,31)
- Pleural effusion is considered a late manifestation of primary TB, occurring in 25% of cases. It is rare in childhood.⁽²⁸⁾

Post-primary TB

The principal changes in post-primary TB are as follows:

- Parenchymal changes consist of slight, clustered nodular opacities, with ill-defined borders, located primarily in the lung apices as well as in the infraclavicular and interclavicular-hilar regions, corresponding to the apical and posterior region of the upper lobes and to the upper segment of the lower lobes. These changes can progress to a heterogeneous segmental or lobar pattern, being bilateral in up to two thirds of the cases. Local lymphatic dissemination is characterized by interposed lines and bands abutting parenchymal opacities. Bronchogenic dissemination is characterized by small, clustered linear and nodular opacities (better identified using HRCT). The classic pattern of post-primary TB is cavitation, single or multiple, measuring, on average, approximately 2 cm in diameter and preferentially located in the apical and dorsal segments. Rarely does it contain an air-fluid level. After cure, these lesions become fibrotic, eventually calcified, being accompanied by distortion of the parenchymal architecture, traction bronchiectasis, deviation of the mediastinal structures, and tuberculomas.⁽²⁸⁻³⁰⁾ The atypical presentations are located in the anterior segments of the upper lobes and in the basal segments. The radiographic manifestations of TB/HIV co-infection depend on the degree of immunosuppression. In those individuals with CD4 counts

below 200 cells/mm³, chest X-ray findings can be normal in up to 20% of cases.

- Airway changes consist of bronchial involvement, characterized by stenosis with resultant atelectasis, in 9-40% of cases.^(28,29)

HRCT

In cases of SRD in which sputum smears are negative for AFB or in which patients are unable to produce material for mycobacteriology tests, HRCT can be indicated when chest X-ray findings are insufficient to establish a diagnosis. The principal alterations are air-space nodules or acinar nodules accompanied by linear ramifications, resulting in a tree-in-bud pattern. Acinar opacities translate the granulomatous inflammatory changes in the terminal bronchioles and alveolar ducts. Although acinar opacities are observed by chest X-ray in half of the TB cases, HRCT can demonstrate them in up to 98% of cases. Other findings include bronchial wall thickening, bronchial wall dilatation and approximation of the bronchial walls. Regarding miliary TB, HRCT, although not highly specific, is more sensitive than is chest X-ray in the definition and distribution of micronodules, as well as in mediastinal evaluation. Parenchymal opacities, small cavitations, acinar nodules, lymph node enlargement and concomitant pleural effusion can be seen.^{(29,31),(32[4]),(33[2B])}

Diagnosis of AFB-negative TB

In countries with limited financial resources, a course of nonspecific antibiotic therapy is indicated (the use of fluoroquinolone should be avoided due to its potential effect on mycobacteria) in order to rule out bacterial infection. There is no scientific evidence to justify two successive courses of nonspecific antibiotics in outpatient cases. Theoretically, therapeutic tests with anti-TB drugs are not indicated as a diagnostic tool. Nonspecific tests, such as inflammatory markers (C-reactive protein, ESR, etc.), do not have good accuracy. Although algorithms/score systems are useful in the management of cases, they have yet to be validated for use in adults in different epidemiological contexts.^(34[2B])

Diagnosis of extrapulmonary TB

Although extrapulmonary TB is paucibacillary, bacteriological diagnosis (as well as histopatho-

logical diagnosis) should be attempted. All of the material obtained by biopsy should also be stored in distilled water or saline solution (both sterile) in order to enable culture.

Pleural TB

Culture combined with histopathological examination of the pleural fragment allows the diagnosis in up to 90% of cases.^(35[2B]) The determination of ADA levels is the principal supplementary method, being part of a set of parameters that authorize the initiation of treatment: exudates containing more than 75% of lymphocytes; ADA > 40 U/L; and absence of neoplastic cells.^{(36[2B]),(37[1A]),(38[2B]),(39[2B])} The Giusti method or another validated method should be used to determine ADA levels.^(40[1B]) Although the determination of IFN- γ levels is supported by good evidence, its cost is too high.^(41[2B]) Among the molecular methods, nested PCR is potentially useful, although there is no evidence for clinical use. In HIV-negative individuals, induced sputum culture is positive in 50% of cases, even when chest X-ray reveals no alterations other than pleural effusion, reaching 75% in HIV-positive individuals.^(35[2B])

Peripheral lymph node TB

Lymph nodes can develop fistulas, releasing secretion in which smear examination for AFB can be positive. Lymph node puncture/biopsy is indicated, and its product should be sent for histopathological analysis, direct microscopy, and culture for mycobacteria.⁽⁴²⁾ Although nested PCR is the molecular method that performs best, there are no studies on its accuracy in routine use.^{(43[1A]),(44[1B])}

CNS-TB

This type of TB can present as meningeal TB (basal, exudative meningitis) or as cerebral parenchymal TB (tuberculoma, abscess, and inflammation of the brain). In suspected cases of CNS-TB, chest X-ray is indicated (X-ray findings are suggestive of TB in half of the cases). Contrast-enhanced neuroimaging (CT or magnetic resonance imaging) should be the first test to be performed. The three most common imaging findings in TB meningitis are hydrocephalus, basal meningeal thickening, and cerebral parenchymal infarction. Lumbar punc-

ture (after CT evaluation) shows the following: pleocytosis (rarely > 1,000 cells/mm³); leukocyte counts ranging from 100 to 500/mm³, with a predominance of lymphocytes; high protein levels (100 to 500 mg%); and low glucose levels (< 40 mg%). The differential diagnosis should be causes of lymphocytic meningitis, and clinical suspicion, epidemiological history, and evaluation of the immunological status of the patients are essential.^(45[2A]) Examination of cerebrospinal fluid for AFB is positive in 5–20% of cases, although positivity can reach 40% if the cerebrospinal fluid is centrifuged. Culture is positive in half of the cases. The use of automated culture methods, such as BACTEC MGIT 960, can increase yield, and results are obtained in 2–3 weeks.

Therapeutic tests are valid after other causes of lymphocytic meningitis are ruled out by clinical and laboratory evaluations.^{(45[2A]),(46[1B])} Although there is no conclusive evidence to support their routine use, as there is for the determination of IFN- γ levels, NAA and the determination of ADA levels in cerebrospinal fluid are promising.

Urinary tract TB

The classic finding is aseptic leukocyturia. Isolated hematuria is uncommon.^(47[2B]) A positive urine culture defines the diagnosis. At least three (up to six) morning samples of urine should be collected and sent to the laboratory on the day of collection. Radiological findings range from small calcifications to obstructive phenomena accompanied by hydronephrosis.^{(48[3B]),(49[2B])} Excretory urography is indicated in cases of suspected urinary tract TB. Cystoscopy and biopsy are important for the diagnosis of cystitis. The use of NAA and ADA level determination has yet to be validated.^(41[2B])

New techniques for the diagnosis of TB

Molecular methods

Molecular tests for the diagnosis of TB are based on the amplification and detection of specific nucleic acid sequences of the Mtb complex in clinical specimens, providing results in 24–48 h. The systems developed in research laboratories are manually operated and are known as in-house systems. Some systems are already commercially available in the form of

standardized kits.^{(50[2A]),(51[2A]),(52[1A])} The accuracy of the different in house methods of NAA for the diagnosis of pulmonary TB is heterogeneous.^(53[1A]) In AFB-positive smear samples, commercial methods have a high sensitivity (96%) and a high specificity (85%), whereas, in AFB-negative smear samples, these methods have a limited sensitivity (66%), despite having a high specificity (98%).^(53[1A]) In clinical practice, NAA tests allow the early diagnosis of TB in approximately 60% of AFB-negative cases (with subsequent positive cultures) and the differentiation between TB and NTM in patients with AFB-positive smears (in regions with a high prevalence of pulmonary disease caused by NTM).

The FDA has approved NAA tests exclusively for use in respiratory samples, that is, for the investigation of pulmonary TB. These tests should not be used to monitor treatment, nor do they replace culture for mycobacteria.⁽⁵⁴⁾

Studies on the accuracy of new methods, such as the GenoType[®] MTBDR strip assay (Hain Lifescience GmbH, Nehren, Germany) and the GeneXpert[®] System (Cepheid, Sunnyvale, CA, USA), are being conducted in Brazil in order to validate the use of these methods for diagnosis.

Serological methods

There are no standardized or validated methods for the diagnosis of pulmonary or extrapulmonary TB.

New techniques to assess drug susceptibility

The only new test recommended by the WHO for routine use is the GenoType[®] strip assay, which identifies the Mtb complex as well as its resistance to H and R.^(51[2A]) This test is based on the detection of the most common mutations in the *rpoB* and *katG* genes. Phenotypic methods based on colorimetric indicators have yet to be approved by the WHO. However, since some of them are very simple and have accuracy similar to that of the proportion method, they are widely used. Among these methods, the one known as nitrate reductase assay is the most promising, since results are obtained more rapidly than when using the other classic phenotypic methods.^{(54[1B]),(55[1A])}

Determination of cytokine levels

The alternative for the diagnosis of latent TB infection, which is currently based on TST results, are the assays known as IGRA. Currently, two of these tests are commercially available: QuantiFERON[®]-TB Gold (Cellestis Inc., Valencia, CA, USA) and T-SPOT[®].TB (Oxford Immunotec, Abingdon, UK). In Brazil, IGRA has yet to be validated for routine use.^{(56[1B]),(57[1A])}

Latent Mtb infection

Latent Mtb infection, or LTB, is the period between the moment at which the bacilli enter the organism and the onset of active TB, providing the opportunity to adopt pharmacological measures, which are currently known as treatment of LTB, replacing the term previously used: chemoprophylaxis.

The diagnosis of LTB is based on positive TST results in combination with the exclusion of active TB. In recent years, the release of IFN- γ when lymphocytes of the individual investigated are exposed to bacillary fragments not present in BCG (see "Determination of cytokine levels" under the heading "New diagnostic methods") have been studied.

The size of the induration on the PPD/TST guides the need for treatment of LTB in the different epidemiological contexts, as presented in Chart 4. A recent study conducted in Brazil demonstrated that recent TB contacts who are 12 years of age or older, are HIV negative, and have a TST induration ≥ 5 mm have a six-fold higher risk of presenting LTB than do contacts with a TST induration < 5 mm; in addition, those authors demonstrated that a TST cut-off point of 5 mm can be used even in regions with a high prevalence of TB.^(58[2B])

Although there are various definitions of "contact" in the literature, the definition based on scientific evidence is that by Rose (exposure to AFB-positive cases for at least 200 h or exposure to culture positive cases for 400 h, and only exposure in enclosed spaces is valued).⁽⁵⁹⁻⁶¹⁾

Immunocompromised patients, patients who were cured from the disease without pharmacological treatment, lung surgery candidates suspected of or confirmed as having a previous disease and transplant candidates should be included in this group. The treatment of LTB in

Chart 4 - Indications for treatment of LTB by TST induration and by risk group.^{(59),(85),(86[1A]),(88)}

TST induration \geq 5 mm
being infected with HIV
having been in contact with a case of pulmonary TB within the last 2 years and having been vaccinated with BCG more than 2 years prior
not having been treated for TB and having sequelae of lesions on chest X-ray
being a transplant candidate or a transplant recipient
being immunocompromised due to other reasons (use of \geq 15 mg/day of prednisone or equivalent for more than 1 month or being a candidate for the use of TNF- α inhibitors)
TST conversion
being a worker in the prison system or an elderly care worker
being a mycobacteriology laboratory staff member
being a health care professional
having had contact with a case of pulmonary TB recently regardless of one's age
TST induration \geq 10 mm
having been in contact with a case of pulmonary TB within the last 2 years and having been vaccinated with BCG 2 or less than 2 years prior
being an intravenous drug user
being immunocompromised due to insulin-dependent diabetes mellitus, silicosis, lymphoma, or neoplasms in the head, neck, and lungs; or due to procedures such as gastrectomy, hemodialysis, and gastrointestinal bypass
being indigenous
Regardless of the TST result
being HIV positive and having been in contact with a case of infectious pulmonary TB within the last 2 years or having sequelae of lesions from pulmonary TB on chest X-ray without a history of treatment for TB, regardless of the TST result (even with an induration $<$ 5 mm)

pregnant women and in indigenous populations follows the same rules.

It is important to point out the following:

- There is no need to evaluate the booster effect in health care workers or in individuals who have been in contact with a TB case.^{(62),(63[2B]),(64[2B])}
- In risk groups (such as that of patients treated with anti-TNF- α drugs or that of patients infected with HIV), TST should be performed periodically in individuals who have an initial negative TST result.
- Individuals who have been in contact with a TB case recently and have a negative TST result (induration $<$ 5 mm) should undergo a second TST at 6-12 weeks after the first one to determine whether there was TST conversion.
- Candidates for the use of TNF- α inhibitors should have received treatment for LTB for at least one month before initiating TNF- α inhibitor therapy.
- The protection provided by the treatment of LTB to individuals who have been in contact with a TB case lasts practically a

lifetime (except in cases of reinfection), although it is more pronounced in the first years.^(65[1B])

Treatment of LTB

Treatment of LTB is indicated for the groups presented in Chart 4, for asymptomatic individuals, and for individuals with normal X-ray findings.⁽⁶⁶⁾ The drug currently used is H at a dose of 5-10 mg/kg of body weight (up to 300 mg/day) for 6 months; extending treatment to 9 months brings few advantages in terms of likelihood of future disease.⁽⁶⁷⁾ The possibility of the diagnosis of active TB should always be ruled out before treatment of LTB is initiated.

Adverse effects

Adverse effects are rare and, in general, do not determine treatment discontinuation. Contrary to what was once thought, liver disease rarely occurs, there being no need for follow-up laboratory testing.^{(68[2C]),(69[2C])} Gastric complaints, urticaria, memory impairment, learning difficulties, excessive sleepiness, insomnia, handwriting

changes, etc, are also uncommon.^(68[2C]) Since the bacillary population in those individuals is small, there is no risk for the development of resistant strains during treatment of LTb with H.

Laboratory tests prior to and after treatment of LTb

The indications for laboratory tests prior to and after treatment of LTb are the same as those pointed out in “Treatment of TB in liver disease”, presented under the topic “TB in special situations and comorbidities (including HIV)”. The discontinuation of H is indicated in cases of ALT > 3 times ULN, if accompanied by signs or symptoms, and in cases of ALT > 5 times ULN, even in asymptomatic patients.

The possibility of shorter treatments is desirable, and, in this sense, some alternatives have been suggested. The combination RZ for 2-3 months is contraindicated due to the high risk of liver disease and death. The combination HR for 3 months or the use of R alone for 2-4 months has proven efficacious, being associated with minimal toxicity, and can be indicated for those who are intolerant to H.^(70[2A])

Individuals who have been in contact with cases of resistant strains should be submitted to treatment of LTb, although there is no scientific evidence regarding the best regimen. The combination EZ or the combination E+fluoroquinolone has been recommended if there is resistance to H and to R; logic indicates that individuals who

have been in contact with cases of MDR-TB should be treated with drugs to which the bacilli are susceptible, even with those drugs presenting lower bactericidal or bacteriostatic activity.^(71[2C])

The need for repeating treatment of LTb should be considered under two conditions:

- persistence of immunosuppression (every 2 or 3 years)
- reexposure to infectious cases (whenever it occurs)

Treatment of TB

The system of TB treatment that has been recommended by the NTCP/NMH since 1979, with the introduction of R and the unification of activities, is being changed. The principal changes proposed by the TAC of the NTCP/NMH are as follows:

- Introduce a fourth drug, i.e., E, in the attack phase (2RHZE/4RH regimen).
- Use fixed-dose combination tablets containing four drugs (RHZE) during the intensive care phase and containing two drugs (RH) during the continued treatment.
- Use tablet formulations as replacements for the capsules previously available.
- Adjust the doses of H and Z in adults to 300 mg/day and 1,600 mg/day, respectively.

Therefore, the TB treatment regimens recommended by the NTCP will be as follows:

Chart 5 – Basic regimen for the treatment of TB in Brazil.

Regimen	Drugs	Body weight	Dose	Months
2RHZE Intensive care phase	RHZE	Up to 20 kg	R: 10mg/kg/day H: 10 mg/kg/day Z: 35 mg/kg/day E: 25 mg/kg/day	2
		20-35 kg	2 tablets	
		36-50 kg	3 tablets	
		> 50 kg	4 tablets	
4 RH ^a Maintenance phase	RH	Up to 20 kg	R: 10 mg/kg/day H: 10 mg/kg/day	4
		20-35 kg	2 tablets	
		36-50 kg	3 tablets	
		> 50 kg	4 tablets	

The number before the acronyms indicates the duration of treatment in months; dose per tablet: R = 150 mg; H = 75 mg; Z = 400 mg; and E = 275 mg. ^aIn the first months of implementation of the new regimen, the maintenance phase will continue in the form of capsules.

Basic regimen (2RHZE/4RH)

The basic regimen is indicated for all new cases of all forms of pulmonary and extrapulmonary TB (with the exception of meningoencephalitis), as well as for all cases of recurrence and retreatment due to noncompliance (Chart 5).

The NTCP also proposes that patients with AFB-positive smears at the end of the second month of treatment should be submitted to culture and identification of mycobacteria, as well as to susceptibility testing, due to the possibility of resistant TB.

Regimen for meningoencephalitis (2RHZE/7RH)

In meningoencephalitis, it is recommended that an oral corticosteroid (prednisone at a dose of 1-2 mg/kg/day for 4 weeks) or, in severe cases, an intravenous corticosteroid (dexamethasone at a dose of 0.3-0.4 mg/kg/day for 4-8 weeks) be used concomitantly, the dose being tapered over the following 4 weeks (Chart 6).⁽⁷²⁾

Regimen for children

For children (patients under 10 years of age), the current treatment with three drugs continues to be used: R (10 mg/kg); H (10 mg/kg); and Z (35 mg/kg). New formulations in the form of dispersible tablets are being developed. One of the explanations for not using E in children is the difficulty in identifying optic neuritis (an

adverse effect of the use of E) early in this age bracket.

Other proposals of the TAC/NMH

Regimen for MDR-TB (2S₅EOZT/4S₃EOZT/12EOT)

The regimen will be standardized, comprising five drugs (SEOZT) during the intensive care phase and three drugs (EOT) during the maintenance phase, as detailed in Chart 7.

In the first 2 months, S should be used 5 times a week, subsequently being used 3 times a week in the following 4 months. The 18-month treatment regimen should be supervised and monitored at a tertiary referral center.^{(73[2B]),(74)} There is some argument as to the use of fluoroquinolone (a mandatory component of MDR-TB treatment regimens). Being less costly, and based on the experience gained from the 3,900 cases registered in the NMH MDR-TB reporting database, O is an option. Levofloxacin and moxifloxacin are also being considered. However, the lack of studies on long-term use of moxifloxacin and the evidence suggesting this drug as a future alternative to reduce treatment duration in treatment-naïve patients speak against the use of moxifloxacin in MDR-TB patients.^(75[1B]) Further studies are needed to compare regimens containing O and regimens containing levofloxacin for the treatment of MDR-TB.

Chart 6 - Treatment regimen for meningoencephalitis.

Regimen	Drugs	Body weight	Dose	Months
2RHZE Intensive care phase	RHZE	Up to 20 kg	R: 10 mg/kg/day H: 10 mg/kg/day Z: 35 mg/kg/day E: 25 mg/kg/day	2
		20-35 kg	2 tablets	
		36-50 kg	3 tablets	
		> 50 kg	4 tablets	
7RH ^a Maintenance phase	RH	Up to 20 kg	R: 10 mg/kg/day H: 10 mg/kg/day	7
		20-35 kg	2 tablets	
		36-50 kg	3 tablets	
		> 50 kg	4 tablets	

The number before the acronyms indicates the duration of treatment in months; dose per tablet: R = 150 mg; H = 75 mg; Z = 400 mg; and E = 275 mg. ^aIn the first months of implementation of the new regimen, the maintenance phase will continue in the form of capsules.

Chart 7 - Regimen for MDR-TB.

Regimen	Drug(s)	Body weight	Dose	Months
2S ₅ OZT Intensive care phase (1st stage)	S	Up to 20 kg	20 mg/kg/day	2
		20-50 kg	500 mg/day	
		> 50 kg	1,000 mg/day	
	E	Up to 20 kg	25 mg/kg/day	
		20-50 kg	800 mg/day	
		> 50 kg	1,200 mg/day	
	O	Up to 20 kg	10 mg/kg/day	
		20-50 kg	400 mg/day	
		> 50 kg	800 mg/day	
	Z	Up to 20 kg	35 mg/kg/day	
		20-50 kg	1,000 mg/day	
		> 50 kg	1,500 mg/day	
T	Up to 20 kg	250 mg/day		
	20-50 kg	500 mg/day		
	> 50 kg	750 mg/day		
4S ₃ EOZT Intensive care phase (2nd stage)	S	Up to 20 kg	20 mg/kg/day	4
		20-50 kg	500 mg/day	
		> 50 kg	1,000 mg/day	
	E	Up to 20 kg	25 mg/kg/day	
		20-50 kg	800 mg/day	
		> 50 kg	1,200 mg/day	
	O	Up to 20 kg	10 mg/kg/day	
		20-50 kg	400 mg/day	
		> 50 kg	800 mg/day	
	Z	Up to 20 kg	35 mg/kg/day	
		20-50 kg	1,000 mg/day	
		> 50 kg	1,500 mg/day	
T	Up to 20 kg	250 mg/day		
	20-50 kg	500 mg/day		
	> 50 kg	750 mg/day		
12EOT Maintenance phase	E	Up to 20 kg	25 mg/kg/day	12
		20-50 kg	800 mg/day	
		> 50 kg	1,200 mg/day	
	O	Up to 20 kg	10 mg/kg/day	
		20-50 kg	400 mg/day	
		> 50 kg	800 mg/day	
	T	Up to 20 kg	250 mg/day	
		20-50 kg	500 mg/day	
		> 50 kg	750 mg/day	

The number before the acronym indicates the duration of treatment in months; the subscript number after a letter in the acronym indicates the number of days in the week when the drug will be administered.

The indications of 2S₅EOZT/4S₅EOZT/12EOT are as follows:

- Failure of the basic regimen, with resistance to R + H or to R + H + another first-line drug.
- Impossibility of using the basic regimen due to intolerance to two or more drugs.

Notes

- If S cannot be used, use amikacin at the same frequency.
- In suspected cases of failure, extend the use of the basic regimen until the culture and susceptibility testing results are known. In addition, consider the following possibilities: (a) infection with NTM; (b) error in drug dosage; (c) irregular use of drugs in cases of self-administered regimens; and (d) poor drug absorption (rarer).
- Regimen for extensive drug resistance (XDR-TB)
- Patients should be referred to tertiary referral centers, and individualized salvage drug regimens should be used. The following drugs will be made available in such referral centers: capreomycin; moxifloxacin; PAS; and ethionamide.

Regimen for polydrug-resistant TB

Regimens should be individualized based on susceptibility testing results.

Regimen for cases of intolerance to one drug

- Intolerance to R: 2HZES₅\10HE
- Intolerance to H: 2RZES₅\7RE
- Intolerance to Z: 2RHE\7RH
- Intolerance to E: 2RHZ\4RH

Regimen for cases of liver disease prior to or during treatment

See “TB in special situations and comorbidities (including HIV)”.

Final recommendations of the TAC/NMH

- All cases of failure or of MDR-TB, in addition to those cases requiring special regimens, should be referred to referral centers, should be reported to the MDR-TB

System, and should be registered in the SINAN.^(73[2B])

- Until the combination tablets containing four drugs are available and the NTCP health care workers have been trained, the RHZ regimen continues to be recommended.
- Drugs in individual formulations in the form of tablets (R, 300 mg; R, 150 mg; H, 100 mg; H, 300 mg; Z, 500 mg; and E, 400 mg) and suspension (R at 2% and Z at 3%) will continue to be available for inclusion in special regimens.
- For cases of TB/HIV co-infection requiring ARV therapy incompatible with the use of R (protease inhibitors), rifabutin will be available to replace R in the composition of the basic regimen.

Comments on the proposals of the NTCP

The principal change in TB treatment presented in the technical note of the TAC/NTCP/NMH (add E to the RHZ regimen) is a consequence of the data collected in the II National Survey on anti-TB Drug Resistance (2007-2008), which showed that the rate of primary resistance to H increased from 3.5% to 6.0% and the rate of primary resistance to R increased from 0.2% to 1.5% between 1997 (I National Survey on anti-TB Drug Resistance) and 2007 in Brazil (National Ministry of Health. II National Survey on anti-TB Drug Resistance, 2008 – unpublished data). The risk of treatment failure in TB patients with initial resistance to H or to R who are treated with RHZ (which is the regimen currently used) exists but is low. However, the risk of disease recurrence is higher than the usual risk, which is approximately 50%.^{(76),(77[2B]),(78[2B]),(79[2B])} The choice of E as the fourth drug is based on data from clinical trials that were conducted in the 1960s and 1970s and demonstrated that R, S, and E were the drugs that, combined with H, had the greatest capacity to reduce treatment failure due to the development of resistant strains.⁽⁸⁰⁾ Therefore, the addition of E to the regimen practically eliminates the risk of failure and reduces the risk of recurrence in patients with primary resistance to H or to R. However, the addition of E does not change the rates of failure or recurrence in patients who have other patterns of resistance.⁽⁷⁶⁾ Furthermore, the RHZE

regimen has long been used, with the same objectives, in virtually all countries

The use of fixed-dose combination (FDC) tablets containing anti-TB drugs has been recommended by the WHO and the IUATLD as an additional measure to improve treatment adherence by reducing the number of tablets to be taken.^(81,82) In a meta-analysis published in 2007, researchers found two studies on TB comparing adherence to treatment with FDC drugs and adherence to treatment with individual tablets between 1966 and 2005.^(83[2A]) In both studies, the use of FDC drugs reduced the risk of noncompliance with treatment by approximately 11%, although the 95% CIs were very wide (both spanning 1, that is, the null effect). The advantages of FDC drugs are as follows: (a) fewer prescription errors; (b) smaller number of tablets; and (c) the impossibility of patients being able to choose the drug to be taken. The principal disadvantages of combining three or more drugs in one tablet that have been described are as follows: (a) possibility of overdosage or underdosage resulting from a prescription error; (b) changes in the bioavailability of R; and (c) difficulties in determining, in cases of adverse effects, which drug is responsible for such effects. In addition, it remains unclear whether there are absorption problems in HIV-positive patients (especially in those with low serum CD4 levels), as can occur even when using drugs in individual tablets.^(84[2B]) Therefore, the present Guidelines recommend that studies based on data collected in accordance with the codes of Good Clinical Practice be conducted in some centers in order to evaluate the impact of the changes.

The Tuberculosis Trials Consortium Study 22 demonstrated that, in the control arm (intermittent RH treatment twice a week during the continued treatment), 21% of the patients with X-ray findings of cavitation and positive culture results at the end of the second month had TB recurrence, compared with only 6% of the patients with X-ray findings of cavitation or positive culture results at 2 months and with 2% of the patients without cavitation or positive culture results.^(85[1B]) Unpublished data from a secondary study of a clinical trial demonstrated that 25% of patients with TB susceptible to all drugs and 24% of patients with TB resistant to at least one drug in the RHZE regimen had

AFB-positive smears at the end of the second month of treatment, showing that there is no relationship between the results of sputum smear examination for AFB and resistance.^(75[1B]) Therefore, there is no scientific evidence to support the recommendation of culture and susceptibility testing only for patients with AFB-positive smears at the end of the second month of treatment.

TB in special situations and comorbidities (including HIV)

TB/HIV

Infection with HIV increases the risk of developing TB significantly, and even patients on ARV therapy have a high incidence of TB.⁽⁸⁶⁾

In HIV-positive patients, the yield of sputum smear examination for AFB is lower, the prevalence of NTM infection is higher, and the incidence of MDR-TB is higher.^{(74),(87[2C])} Therefore, in addition to smear examination for AFB, culture, identification, and susceptibility testing should be requested.

In patients with TB/HIV co-infection, TB treatment should be prioritized and, when indicated, ARV therapy should be initiated 2-4 weeks after the initiation of TB treatment. The regimens recommended are the same as those for HIV-negative patients (see "Treatment of TB"), with the possibility of replacing R with rifabutin in patients on ARV therapy incompatible with R.^(88,89) The best option for the composition of the ARV regimen is efavirenz combined with two NRTIs, and no dosage change is required when it is administered together with R.^(89,90)

The occurrence of IRIS is not an indication for discontinuing any of the treatments. The management of IRIS includes the use of corticosteroids in more severe cases.^(89,90)

LTB

See "Latent Mtb infection".

TB in diabetics

Consider extending treatment to 9 months and replace oral hypoglycemic agents with insulin during treatment (keep fasting glycemia ≤ 160 mg/dL).

TB in pregnant women

Pyridoxine (50 mg/day) is indicated during pregnancy, given the risk of H causing convulsive seizures in neonates. The RHZE regimen can be administered in the usual doses. However, R should not be administered in increased doses in intermittent regimens due to the risk of hypoprothrombinemia and bleeding. The use of Et, S, and quinolones in pregnant women is contraindicated.^(89,91,92)

TB in renal failure

R, H, and Z are safe and can be prescribed in the usual doses. The treatment is changed exclusively in cases of renal failure with creatinine clearance ≤ 30 mL/min or in cases of renal failure requiring dialysis. It is recommended that S and E be avoided. If there is no other alternative, S and E should be administered at lower doses and at longer intervals. The safest regimen is 2HRZ/4HR.⁽⁸⁹⁾ If the basic regimen cannot be used, other drugs are recommended (Chart 8).

Liver disease and TB

Request laboratory tests (determination of ALT/AST, bilirubin, and alkaline phosphatase levels) at the initiation of and during treatment of adult patients with a history as follows:

- alcohol consumption
- (past or current) liver disease or hepatitis
- current use of other hepatotoxic drugs
- infection with HIV

In cases of hepatitis or liver disease without an apparent etiologic factor, also request analysis of viral hepatitis markers. An increase in alkaline phosphatase or bilirubin levels, with little or no increase in ALT (previously known as glutamic-pyruvic transaminase—GPT) levels, indicates cholestasis. An increase in ALT (GPT) levels is

more specific for hepatocellular lesion than is an increase in AST (also known as glutamic-oxaloacetic transaminase—GOT) levels, which can also be indicative of muscle abnormalities, as well as of abnormalities in the heart or in the kidney.

Treatment of TB and liver disease^(1,88,93,94)

Liver disease prior to the initiation of treatment

Stable or unstable liver disease (but without cirrhosis) + tests at baseline (prior to the initiation of treatment) revealing the following:

- ALT/AST > 3 times ULN = RHE for 9 months
- ALT/AST ≤ 3 times ULN = RHZE for 6 months
- Liver cirrhosis = RE + (levofloxacin or moxifloxacin or O or cycloserine) for 12-18 months
- Established chronic liver disease
 - › Without any clinical evidence of disease and presenting ALT/AST ≤ 3 times ULN
 - » RHZE normally (even if patients are infected with the hepatitis virus or have a history of acute hepatitis or excessive alcohol consumption). Follow-up evaluations should include periodic laboratory tests.⁽⁸⁸⁾
 - › With clinical evidence of disease or presenting ALT/AST > 3 times ULN
 - » 2HRES/6HE or 2HRE/6HE or 2HSE/10HE or 3SEO/9EO

Notes

- R is hepatotoxic, as are H and Z. However, of the three, R causes the least hepatocellular injury (although it can cause cholestatic jaundice) and Z is the most hepatotoxic. Given the efficacy of H and, especially, of R, their use can always be attempted, even in the presence of preexisting liver injury.^(89,95,96)
- Hepatotoxicity is caused by the pair R+H. Rarely does R alone cause hepatic changes. Therefore, in theory, the 2RSE/7RE or the 6RE+levofloxacin regimen can also be an alternative, although there is no scientific evidence to support the use of any of these two regimens.
- Rarely does E cause liver injury.

Chart 8 - Treatment of TB in advanced renal failure.^{(87)(2C)}

Drug	Dose and frequency
Isoniazid	300 mg/day or 900 mg/3 times a week
Rifampin	600 mg/day or 600 mg/3 times a week
Pyrazinamide	25-35 mg/kg/dose/3 times a week
Ethambutol	15-25 mg/kg/dose/3 times a week
Ethionamide	250-500 mg/dose/daily
Streptomycin	12-15 mg/kg/dose/2-3 times a week
Amikacin	12-15 mg/kg/dose/2-3 times a week

Acute hepatitis

If the initiation of TB treatment cannot be delayed until hepatitis is resolved, prescribe 3SE/6RH or 3SEO/6RH (in extensive TB). Administer O in a single morning dose. The dose for patients weighing 45 kg or less is 400 mg/day. For patients weighing more than 45 kg, there is evidence to support the use of 400 mg/day^(97,2B) and the use of 600 mg/day (three 200-mg tablets per day).^(98,2C) Due to the fact that 200-mg O tablets are unavailable and that 400-mg tablets cannot be divided into two halves, some centers prescribe two 400-mg O tablets (800 mg/day) for patients weighing more than 45 kg (apparently without problems), although there is no scientific evidence to support this dosage.

Hepatotoxicity after the initiation of treatment

- ALT/AST > 5 times ULN (with or without jaundice), or jaundice (with or without increased ALT or AST levels), or liver symptoms: discontinue the regimen and investigate alcohol abuse, biliary disease, or use of other hepatotoxic drugs.
- In severe cases, until the cause of the abnormality is identified, or in cases in which enzyme levels or bilirubin levels do not normalize after 4 weeks of treatment, use 3SEO/9EO, combined with H or not.^(97,98)

Reintroduction of the RHZE regimen^(1,88,93,94)

- ALT/AST < 2 times ULN: reinitiate R, H, and Z one at a time. First R (with or without E); 3-7 days after the reintroduction, request tests; if there is no increase in ALT/AST levels, reintroduce H; if, 1 week after the

reintroduction of H, there is no increase in the ALT/AST levels, reinitiate Z.

- If the symptoms reappear or if ALT/AST levels increase, discontinue the last drug added.
- In patients with long-term or severe hepatotoxicity, do not reintroduce Z and extend treatment to 9 months.

Notes

- There can be a transitory increase in ALT/AST levels during the first weeks of treatment with the RHZE regimen. Only discontinue the regimen if any of the following occur: a > 3 times ULN increase in ALT/AST levels accompanied by symptoms (anorexia or malaise or vomiting); a > 5 times ULN increase in ALT/AST levels, with or without symptoms; or an increase in bilirubin (or clinical jaundice) or alkaline phosphatase levels.
- Hepatic changes can be caused by TB and improve after the initiation of treatment.
- If there is a history of alcoholism, use pyridoxine (50 mg/day) to prevent peripheral neuritis.

Transplant recipients, patients with silicosis or malignant neoplasia, or patients on immunosuppressive drugs

Treatment can be extended to 9 months, and follow-up evaluations can be performed for 2 years after cure, by means of quarterly appointments.⁽⁹⁹⁾

New drugs for the treatment of TB

Studies for the development and validations of new anti-TB drugs should have the following objectives:

Chart 9 - Principal anti-TB drugs that have been evaluated in clinical studies.

Drug	Phase of study
Fluoroquinolones	Phase II trials for susceptible TB ^a
Diarylquinoline TMC 207	Phase II trial for MDR-TB ^b
Nitroimidazoles PA-824 and OPC-67683	PA-824: phase IIa trial for susceptible TB ^a
	OPC-67683: phase II trial for MDR-TB ^a
Linezolid	Phase IIa for susceptible TB and IIb for MDR-TB ^a
Ethylenediamine Q109	Phase I ^b
Pirrol LL-3858	Phase I ^b

^acompleted; and ^bunderway.

- reduce the duration of treatment of active TB and LTB
- reduce the interaction between anti-TB drugs and ARV agents
- find therapeutic alternatives for the treatment of MDR-TB

The main TB treatment drugs that have been evaluated in clinical trials are listed in Chart 9.

It has been demonstrated that fluoroquinolones have in vitro and in vivo bactericidal activity against *Mtb*.^(100,101) Clinical studies demonstrated that the addition of a fluoroquinolone to the first-line regimen significantly increased the rate of culture conversion in the second and in the third month of treatment and that the regimens containing moxifloxacin were better than those containing E or O or gatifloxacin. However, there was no difference between the R + moxifloxacin + ZE regimen and the RHZE regimen.^{(75[1B]),(101[1B]),(102[1B])} Therefore, moxifloxacin is potentially useful in therapeutic regimens in order to reduce treatment duration. Recently completed clinical trials with fluoroquinolones are listed in Chart 10.

Surgical treatment of pulmonary TB

The main surgical indications in cases of pulmonary TB are as follows:

- MDR-TB
- severe adverse effects to anti-TB drugs
- uncontrolled or recurrent hemoptysis
- complications, including empyema, pneumothorax, and bronchopleural fistula
- lymph node enlargement with compression of the tracheobronchial tree

The indications for surgical treatment without active TB (sequela or residue) are as follows:

- symptomatic pulmonary residue (hemoptysis or recurrent infections)
- symptomatic cavitary lung lesion colonized by fungi

- uncontrolled or recurrent hemoptysis
- complications, including empyema, pneumothorax, and bronchopleural fistula
- differentiation between TB and lung cancer

MDR-TB

The surgical indications in MDR-TB are as follows^{(103[3B]),(104[3B]),(105[3B]),(106[3B]),(107[3B]),(108[3B]),(109[3B])}:

- a) persistence of positive sputum smears
- b) cases of localized disease, usually cavitary, with a high risk of recurrence and presenting caverns with no signs of regression during treatment and cases of destroyed lung
- c) profile of significant resistance to at least four drugs
- d) multiple recurrence
- e) recurrent hemoptysis or secondary infection

Sputum conversion prior to surgery or a reduction in the bacterial load is desirable in order to reduce the risk of recurrence. Patients with *Mtb* resistant to nearly all drugs are usually operated on earlier (1-2 months after the initiation of therapy for multidrug resistance). Patients with bacilli susceptible to some of the drugs should be treated for 3-4 months in order to achieve sputum conversion or reduce the bacterial load. The presence of cavitary lesions reinforces the indication for early surgery due to the restricted penetration of the drugs and the larger bacillary load.^{(104[3B]),(105[3B]),(109[3B]),(110[3B])} After surgery, the drugs should be maintained for 18-24 months.^{(104[3B]),(110[3B])} Nutritional status and extent of disease are decisive factors in the success of the surgical treatment. In recent studies, the disease was controlled with adjuvant surgical treatment in up to 98% of cases, surgical mortality ranged from 0 to 3%, morbidity ranged from 6 to 30%,

Chart 10 - Clinical trials of fluoroquinolones.

Trial	Number of patients	Regimen evaluated
Study 27 (CDC/Tuberculosis Trial Consortium)	227	RHZE vs. RHZ+moxifloxacin
OFLOTUB International Consortium	217	RHZE vs. RHZ+moxifloxacin or RHZ+gatifloxacin or RHZ+ofloxacin
Moxi study (Federal University of Rio de Janeiro/Hopkins/FDA)	170	RHZE vs. RHZ+moxifloxacin
Study 28 (CDC/Tuberculosis Trial Consortium) ^a	381	RHZE vs. R+moxifloxacin+ZE

^aUnpublished data.

and the principal postoperative complications were bronchopleural fistula and empyema.^{(103[3B]),(107[3B]),(108[3B]),(110[3B]),(111[3B]),(112[3B]),(113)}

Surgery as adjuvant therapy for cases of XDR-TB was indicated in patients with localized lesion and no initial response to treatment.^{(112[3B]),(113)}

Under some circumstances, surgery can be indicated even in patients with TB susceptible to drugs^{(114[4]),(115[3B])}:

- extreme intolerance to anti-TB drugs
- incomplete treatment, even after several attempts
- uncontrollable massive hemoptysis
- cases of nodular lesions or masses in which it is not possible to rule out malignancy

Hemoptysis

The ideal scenario is to transform the emergency procedure into an elective one by controlling hemoptysis and determining pulmonary function, thereby reducing anesthetic risk, as well as preventing extensive and unnecessary pulmonary resections.^{(114[4]),(115[3B]),(116[4])}

Endobronchial TB

Bronchoscopy for the evaluation of endobronchial disease is indicated in pulmonary TB when there is a significant reduction in lung volume, unexplained chronic cough, hemoptysis, or localized wheezing.^(104[3B]) Bronchoplasty or tracheoplasty are indicated when, despite the use of anti-TB drugs, there is progressive bronchial stenosis. Underused options include the following: dilatation, which can result in resolution in cases of short stenosis; use of stents; and use of laser.

Tuberculous lymphadenopathy

In children with hilar or mediastinal lymphadenopathy, there can be acute or chronic compression of the tracheobronchial tree causing bronchial atelectasis, ulceration, and perforation, as well as lymph node calcification with calculus formation in the bronchi (broncholithiasis), which erode and migrate to the bronchial lumen. Surgical treatment is reserved for cases of clinical treatment failure. Prophylactic removal is not recommended.^(116[4])

Pleural sequelae of TB

The evolution of pleural effusion due to TB is favorable, and lung entrapment is rare. Decortication is considered when there is a significant deficit in pulmonary function and labor capacity. The presence of relevant bronchopulmonary lesions makes decortication impossible.^{(115[4]),(117[4])}

Childhood TB

Diagnosis of active TB

Due to the difficulty in demonstrating Mtb in clinical specimens collected from children, the diagnosis of active TB is based on clinical, epidemiological, and radiological findings associated with the interpretation of TST results, although the infectious agent should be identified whenever possible.^(118[2B])

The clinical manifestations are as follows:

- (moderate evening) fever for 15 days or more or irritability
- cough
- weight loss
- night sweats

Cases of slowly-progressive pneumonia (for 2 weeks or more) with no response to antimicrobial agents are also suspected cases of pulmonary TB.^{(118[2B]),(119[4])} Chest X-ray and TST are indicated in all children suspected of having TB. The most common pattern on chest X-rays is that of primary TB (see “Radiological diagnosis; Primary TB” under the topic “Diagnosis”), with persistent opacities or atelectasis that do not improve with the use of antibiotics. In adolescents, the radiological pattern is similar to that found in adults (with apical infiltrates with or without cavitation or pleural effusion), although it can sometimes be equal to the pattern found in children.^(120[3B]) In daily practice, the diagnosis is made using a scoring system (Chart 11) that has high sensitivity and high specificity in HIV-positive and in HIV-negative children.^{(118[2B]),(121[2B])}

GL should not be routinely performed and is indicated only if the scoring system score is negative for TB and it is possible to perform culture for Mtb.^(122[2B]) The sensitivity of smear examination for AFB ranges from 10 to 15%, whereas the sensitivity of culture ranges from 30 to 50%.^{(123[1B]),(124[2B]),(125[3B])} Bronchoscopy

Chart 11 – Scoring system for the diagnosis of pulmonary TB in children (under 10 years of age) and in adolescents (with AFB-negative smears).

Clinical and radiological profile	Having been in contact with an adult with TB	Tuberculin skin test	Nutritional status
<p>Fever or symptoms such as cough, adynamia, expectoration, weight loss, sweating for more than 2 weeks</p> <p>Add 15 points</p> <ul style="list-style-type: none"> • Hilar lymph node enlargement or military pattern • Condensation or unchanging infiltrate (with or without cavitation) for more than 2 weeks • Condensation or infiltrate (with or without cavitation) for more than 2 weeks, showing worsening or no improvement with the use of antibiotics against common pathogens <p>Add 15 points</p>	<p>Close contact, within the last 2 years</p> <p>Add 10 points</p>	<p>Induration \geq 10 mm in individuals not vaccinated with BCG or vaccinated less than 2 years prior</p> <p>or</p> <p>Induration \geq 5 mm in individuals not vaccinated or vaccinated more than 2 years prior</p> <p>Add 15 points</p>	<p>Severe malnutrition</p> <p>Add 5 points</p>
<p>Asymptomatic or presenting symptoms for less than 2 weeks</p> <p>0 points</p>			
<p>Improvement in respiratory infection with the use of antibiotics against common pathogens or without the use of antibiotics</p> <p>Subtract 10 points</p>	<p>Occasional or negative</p> <p>0 points</p>	<p>Induration < 5 mm</p> <p>0 points</p>	<p>Normal weight or nonsevere malnutrition</p> <p>0 points</p>

Interpretation: score equal to or greater than 40 points → highly likely diagnosis; score ranging from 30 to 35 points → possible diagnosis; and score equal to or lower than 25 points → unlikely diagnosis.

can be useful, although its yield is not higher than that of the collection of three samples of GL.^(126[4]) Sputum induction is a minimally invasive procedure, and its yield has been shown to be higher than that of GL.^{(123[1B]),(124[2B])} The value of serologic tests and interferon-gamma release assays in the diagnosis of TB is discussed under the topic “New techniques for the diagnosis of TB”.

LTB

Chest X-rays and TSTs should be performed in all patients who have been in contact with a case of active pulmonary TB.⁽⁶⁸⁾ In children who have been in contact with a case of pulmonary TB, have no symptoms, and present normal X-ray findings, the TST is considered positive if the induration is ≥ 5 mm (children not vaccinated with BCG or vaccinated more than 2 years prior) or ≥ 10 mm (children vaccinated with BCG 2 or less than 2 years prior). In immunocompromised patients, the TST is considered positive when the induration is ≥ 5 mm, regardless of age or BCG vaccination status. The approach in children who have been in contact with an adult with TB is described in Figure 3. The treatment of LTB is presented under the topic “Latent Mtb infection”.

Extrapulmonary TB

Approximately 20% of TB cases in children present as extrapulmonary TB.^(127[3B]) The most

common forms are peripheral lymph node TB, pleural TB, bone TB, and tuberculous meningoencephalitis.^(127[3B])

Peripheral lymph node TB

Peripheral lymph node TB can present as scrofula or scrofuloderma. It most commonly affects the cervical lymph node chain, unilaterally or bilaterally, and is almost always asymmetric. The lymph nodes are hardened, adhere to each other and to the deep planes, show subacute progression, and can have fistulization. The differential diagnosis includes paracoccidioidomycosis and cat scratch disease. The diagnosis is made by needle aspiration or lymph node biopsy. Lymph node TB is usually paucibacillary, whereas paracoccidioidomycosis involves the presence of a large number of fungi.

Pleural TB

See “Diagnosis of TB”.

Bone TB

Bone TB accounts for 10-20% of extrapulmonary lesions in childhood. The most common manifestations are spondylitis, arthritis, and osteomyelitis. Tuberculous spondylitis affects the intervertebral disk later in the course of the disease, and subligamentous spread of infection can lead to the involvement of multiple vertebral bodies, in a continuous or discontinuous way,

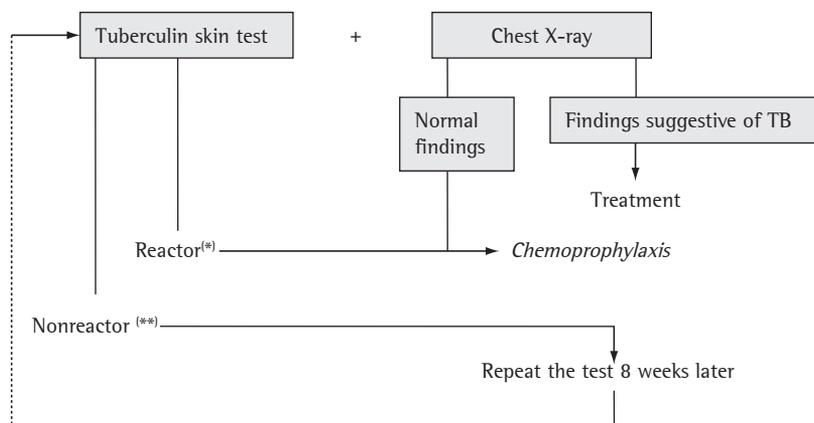


Figure 3 - Approach to children who have been in contact with a TB case. (*)Positive: induration > 10 mm in children vaccinated with BCG less than 2 years prior, or induration > 5 mm in children not vaccinated with BCG or vaccinated more than 2 years prior. When the test is performed twice, a result can be considered positive if the difference between the first and the second test is ≥ 10 mm. (**)Negative: induration less than that of the positive test result.

and to severe thoracic deformity (Pott's disease). Tuberculous arthritis results from metaphyseal spread of infection to the joints. Radiologically, osteomyelitis can present as well-defined cystic lesions, as areas of osteolysis, or as infiltrative lesions. The use of X-ray, ultrasound or HRCT reveals soft tissue involvement, bone sclerosis, and destruction of the posterior elements of the vertebral body. Magnetic resonance imaging can determine early bone marrow involvement and the extent of the lesion into the soft tissues.^(128[3B]) The definitive diagnosis is made by biopsy.

Tuberculous meningoencephalitis

Tuberculous meningoencephalitis shows subacute progression, slower than that of bacterial meningitis. The prodromal stage (lasting from days to weeks) presents fever, worsening of overall health status, and anorexia, which can be accompanied or not by cough. Subsequently, there is headache, vomiting, cranial nerve paralysis (of the second, third, fourth, sixth, and seventh cranial nerves), meningeal signs, paresis, a drop in the level of consciousness, and coma. The diagnostic evaluation in suspected cases of meningoencephalitis due to TB is presented under the topic "Diagnosis of TB".

TB and HIV infection in children

See "TB in special situations and comorbidities (including HIV)".

Immune reconstitution syndrome

In immunocompromised children with a high bacterial load, the initiation of highly active ARV therapy can lead to an immune reconstitution syndrome, with a pronounced inflammatory reaction at the sites affected by Mtb. This syndrome presents fever, weight loss, and lymph node enlargement, as well as pulmonary consolidation and pleural effusion. Histologically, there is granulomatous reaction with or without caseation. Direct microscopy can be positive, and culture is invariably positive.⁽¹²⁹⁾ In South Africa, in children with immune reconstitution syndrome, the duration of ARV treatment ranged from 6 to 105 days and the duration of TB treatment ranged from 21 to 59 days. The children had paradoxical reactions to the treatment of both diseases.^(130[3B])

Treatment

The treatment of TB in children is presented under the topic "Treatment of TB".

BCG vaccination

The BCG vaccine protects against severe manifestations of primary Mtb infection, such as hematogenous dissemination and meningoencephalitis, but it does not prevent Mtb infection.^{(131[1A]),(132[1A])} The BCG vaccine is primarily indicated in children 4 years of age or younger, being mandatory for children less than 1 year of age.^(133[1A]) The aspects regarding conservation, administration, and other technical procedures are described in the NMH guidelines (1994).

BCG vaccination is recommended in the following cases:

- Neonates, whenever possible in the maternity ward, as long as their weight is equal to or greater than 2 kg and there are no clinical complications
- Neonates born to mothers with AIDS
- Children infected with HIV or born to mothers with AIDS, as long as the TST results are negative and they are asymptomatic for this syndrome. The children vaccinated under this condition should be monitored by the epidemiological surveillance network, in referral centers for AIDS.
- Children who have been in contact with a case of leprosy (norms of the NMH Leprosy Control Program). Household contacts, regardless of the clinical form, should receive two doses of the BCG vaccine.

BCG revaccination

The loss of the protective effect of BCG vaccination over time has led some countries to adopt revaccination.^(134[2A]) In Brazil, the NMH recommended BCG revaccination in the population aged 6 to 14 years in 1994. However, studies on BCG revaccination (including those conducted in Brazil) have failed to show that the second dose of BCG provides protection against TB in revaccinated adolescents.^{(134[2A]),(135[3A]),(136[3A]),(137[1A]),(138[1B])} Therefore, in 2006, the NMH recommended the discontinuation of BCG revaccination. Revaccination is not recommended for the indigenous population either. Consequently, in addition to children who have been in contact

with a case of leprosy, only children who do not present a vaccination scar 6 months after the first vaccination should be revaccinated (only once), revaccination being a priority in those under 5 years of age.

Contraindications of BCG vaccination

Relative contraindications are as follows: being a neonate weighing less than 2 kg; having a dermatologic disease, either at the vaccination site or at several sites; being on immunosuppressants or steroids (in such cases, the vaccination will be postponed until the situations indicated have been resolved).

Absolute contraindications are as follows: being an adult infected with HIV (regardless of symptoms) or a symptomatic child; and having primary immunodeficiency with T-cell impairment.

Adverse effects of the BCG vaccine

Adverse effects of the BCG vaccine are rare. Most of them result from imperfect technique, such as deep (subcutaneous) administration, inoculation of an excessive dose, or contamination. When, in the routine of health care facilities, it is observed that there is an increase in the number of cases of adverse effects, it is important to review the training of vaccine providers. The most common complications include abscess at the vaccination site, extremely large ulcers, and fluctuating ganglia with fistulization. Treatment should consist of H (10 mg/kg of body weight, up to 300 mg/day) until lesion regression, in approximately 45 days or more, if necessary. Cold abscesses and fluctuating ganglia can be drained but should not be incised. Keloid scars can occur in genetically prone individuals and would be more common in those who are infected or in those who have been revaccinated. Generalized lesions and BCG disseminated disease, which are also rare, are associated with primary combined immunodeficiency or HIV disease.^(139[1B])

TB and biosafety

It has been demonstrated that, in developed and in developing countries, the rate of TB transmission in enclosed spaces is high, and, therefore, the WHO has proposed that measures to control TB transmission be adopted in the so-called “high-risk environments” (Health Care Clinic or not).^{(140),(141[2B]),(142[2B]),(143[4]),(144[2B]),(145)}

Although the profile of TB in Brazil is mostly that of community transmission, high rates of TB transmission have been observed in medical schools, university hospitals, emergency rooms, prisons, and psychiatric clinics.^{(144[2B]),(146[2B]),(147[2B]),(148[2B]),(149[2B]),(150[2B]),(151[2B]),(152[2B])}

It is estimated that 1-19% of health care workers are infected annually in large hospitals.⁽¹⁴⁰⁾ In a systematic review of studies conducted in low- or middle-income countries, the prevalence and the incidence of LTB in health care workers ranged from 33 to 79% and from 0.5 to 14.3% per year, respectively.^(153[1A])

The measures to control TB transmission should take into account the type of institution and are divided into three groups:

- administrative measures: investigation; early diagnosis and treatment; isolation of suspected cases; and a written plan for infection control
- environmental control (or engineering control) measures: isolation rooms with natural ventilation; rooms with negative pressure; and use of HEPA filters
- respiratory protection measures: use of surgical masks by the patients and use of N95 masks by the health care team

The specific measures for each high-risk environment are described in Chart 12.^{(145,154-156),(157[1A]),(158[4])}

The risk of Mtb infection will be reduced with the combined use of administrative measures, environmental control measures, and respiratory protection measures.

TB and smoking

The association between TB and smoking, as well as the increase in TB infectivity, morbidity, and mortality in active or passive smokers, has been demonstrated. Smoking seems to be associated with delayed sputum smear conversion and higher rates of TB recurrence.^{(161[2B]),(162[2C])}

The estimated prevalence of smoking among TB patients is 52%, much higher than that found in the general population aged 18 years or older (14.5%).^{(163[2C]),(164)} The presence of TB among smokers can result in overloaded public health care facilities in developing countries. An effective strategy to fight smoking can have a positive impact on the reduction of TB incidence and on response to treatment. Therefore, smoking cessation strategies and programs should be incorporated by the NTCP in the treatment of TB patients.

Chart 12 – Specific measures for each high-risk environment.

High-risk environment	Specific measures
Outpatient clinic environment	<ul style="list-style-type: none"> • Waiting rooms and treatment rooms should be adequately ventilated. • The air flow should be directed from the professional to the patient, thereby avoiding the exposure of the professional. • The flow of patients suspected of having TB should be separated from that of the other clinical patients. • Surgical masks should be provided to patients in whom the diagnosis has been confirmed and to patients who are suspected of having the disease—those who are untreated and those who have been treated for less than 2 weeks. • A place, which should be isolated and adequately ventilated (preferably outdoors), should be assigned for sputum collection
Hospital environment - Emergency room	<ul style="list-style-type: none"> • Active surveillance of cases of SRD and use of surgical masks until the diagnosis of TB is ruled out. • Collection of three sputum samples every 8 h, one of which preferably in the morning on an empty stomach. • Chest X-ray. • Isolation of confirmed cases and highly suspected cases. • Specific room, isolated and adequately ventilated (outdoors or with negative pressure), for sputum collection. • Use of N95 masks for the protection of the health care workers who treat the patients.
Hospitalization	<ul style="list-style-type: none"> • Individual room with adequate ventilation. • In cases of MDR-TB, isolation on a separate ward, with adequately ventilated rooms or, preferably, rooms with negative pressure and a HEPA filter to control the outflow of air • Use of N95 respirators by the health care workers. • Use of surgical masks by the patients who have to be transported to another unit. • Adherence to recommendations for up to 2 weeks after the initiation of effective treatment.
Laboratory environment - Waiting room	<ul style="list-style-type: none"> • The waiting room should be adequately ventilated and have directed air flow. • Patients should be provided sterile, wide-mouthed collection vials as well as paper tissues for them to clean their mouths. • All orderlies should wear gloves, masks, and caps. • The samples should be transported from the collection room to the processing room in rigid and unbreakable containers with a sealed lid.
Laboratory environment - Sample preparation room	<ul style="list-style-type: none"> • Sputum smear slides for microscopy should be prepared in a biosafety level 2 room, at least. • Sputum for culture and for procedures in which there is sample concentration by centrifugation or a similar process should be prepared in a biosafety level 3 room equipped with a Class II, type B2 microbiological safety cabinet. • The health care workers should be appropriately attired in impervious lab coats with knit cuffs and back closure, as well as wear slip-resistant shoes, surgical gloves, N95 masks, goggles, and caps. • The waste material produced by the sample handling should be autoclaved and placed in bags displaying with the hazardous material symbol.
Home environment	<ul style="list-style-type: none"> • Patients should be instructed to cover their mouth while coughing. • Patients should sleep in an isolated room for at least 2 weeks of effective treatment. • Patients should avoid enclosed places and crowding in the first 2 weeks of treatment.
Prison environment	<ul style="list-style-type: none"> • Early diagnosis through active surveillance. • Supervised treatment. • Individual cells for patients with AFB-positive smears for at least 2 weeks of treatment.

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References

- World Health Organization. Respiratory care in primary care services – a survey in 9 countries. Geneva: World Health Organization; 2004.
- World Health Organization [homepage on the Internet]. Geneva: the Organization; c2009 [cited 2009 Aug 23]. Ottmani SE. Overview of PAL strategy; 2006. [Microsoft PowerPoint document, 22 slides] Available from: www.who.int/entity/tb/dots/planningframeworks/stb_pal_strategy.ppt
- dos Santos MA, Albuquerque MF, Ximenes RA, Lucena-Silva NL, Braga C, Campelo AR, et al. Risk factors for treatment delay in pulmonary tuberculosis in Recife, Brazil. *MC Public Health*. 2005;5:25.
- Maior M, Golub JE, Chaisson R, Souza GM, Conde MB. Interval of time between the onset of symptoms and the treatment of pulmonary tuberculosis (TB) in two outpatients primary health centers (OPHC) in Nova Iguaçu, Brazil. Preliminary results. In: American Thoracic Society. Proceedings of ATS International Conference; 2007 May 18-23; San Francisco. New York: ATS; 2007; p. A414.
- Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health*. 2008;8:15.
- Fundação Nacional de Saúde. Tuberculose: guia de vigilância epidemiológica. Brasília: Fundação Nacional de Saúde; 2002.
- Bastos LG, Fonseca LS, Mello FC, Ruffino-Netto A, Golub JE, Conde MB. Prevalence of pulmonary tuberculosis among respiratory symptomatic subjects in an out-patient primary health unit. *Int J Tuberc Lung Dis*. 2007;11(2):156-60. Erratum in: *Int J Tuberc Lung Dis*. 2007;11(8):936. Golub, J L [corrected to Golub, J E].
- Santha T, Garg R, Subramani R, Chandrasekaran V, Selvakumar N, Sisodia RS, et al. Comparison of cough of 2 and 3 weeks to improve detection of smear-positive tuberculosis cases among out-patients in India. *Int J Tuberc Lung Dis*. 2005;9(1):61-8.
- American Thoracic Society; Centers for Disease Control and Prevention; Infectious Diseases Society of America. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: controlling tuberculosis in the United States. *Am J Respir Crit Care Med*. 2005;172(9):1169-227.
- Morrone N, Abe NS. Bronchoscopic findings in patients with pulmonary tuberculosis. *J Bronchol*. 2007;14(1):15-8.
- Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. *Int J Tuberc Lung Dis*. 2005;9(11):1183-203.
- Becerra MC, Pachao-Torrealblanca IF, Bayona J, Celi R, Shin SS, Kim JY, et al. Expanding tuberculosis case detection by screening household contacts. *Public Health Rep*. 2005;120(3):271-7.
- Abrahão RM, Nogueira PA, Malucelli MI. Tuberculosis in county jail prisoners in the western sector of the city of São Paulo, Brazil. *Int J Tuberc Lung Dis*. 2006;10(2):203-8.
- Lemos AC, Matos ED, Bittencourt CN. Prevalence of active and latent TB among inmates in a prison hospital in Bahia, Brazil. *J Bras Pneumol*. 2009;35(1):63-8.
- Nagpal DR, Vishwanath MK, Dwarakanath G. A socio-epidemiological study of out-patients attending a city tuberculosis clinic in India to judge the place of specialized centres in a tuberculosis control programme. *Bull World Health Organ*. 1970;43(1):17-34.
- Sung Chin K. Case-finding in the Korean national tuberculosis programme. *Bull Int Union Tuberc*. 1976;51(1):381-2.
- Morrone N. Diagnosis of tuberculosis in individuals with respiratory symptoms: commentary on the II Guidelines of the Brazilian Society of Pulmonology and Phthysiology and the Ministry of Health. *J Bras Pneumol*. 2005(31)4:350-355.
- Becx-Bleumink M, Wibowo H, Apriani W, Vrakking H. High tuberculosis notification and treatment success rates through community participation in central Sulawesi, Republic of Indonesia. *Int J Tuberc Lung Dis*. 2001;5(10):920-5.
- Banerji D, Andersen S. A sociological study of awareness of symptoms among persons with pulmonary tuberculosis. *Bull World Health Organ*. 1963;29:665-83.
- Borgdorff MW, Floyd K, Broekmans JF. Interventions to reduce tuberculosis mortality and transmission in low- and middle-income countries. *Bull World Health Organ*. 2002;80(3):217-27.
- Lemos AC, Matos ED, Pedral-Sampaio DB, Netto EM. Risk of tuberculosis among household contacts in Salvador, Bahia. *Braz J Infect Dis*. 2004;8(6):424-30.
- Larouze B, Sanchez AR, Espinola AB, Pires JD, Capone D, Gerhardt G, et al. Busca ativa sistemática de casos de tuberculose entre ingressos no sistema penitenciário: uma necessidade?. *J Bras Pneumol*. 2008;34(Suppl 1R):R6-R7.
- Legrand J, Sanchez A, Le Pont F, Camacho L, Larouze B. Modeling the impact of tuberculosis control strategies in highly endemic overcrowded prisons. *PLoS One*. 2008;3(5):e2100.
- Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Coordenação Geral do Programa Nacional de Imunizações. Nota Técnica Nº 66/CGPNI/DEVEP/SVS/MS. Brasília: Ministério da Saúde; 2006.
- Conde MB, Soares SL, Mello FC, Rezende VM, Almeida LL, Reingold AL, et al. Comparison of sputum induction with fiberoptic bronchoscopy in the diagnosis of tuberculosis: experience at an acquired immune deficiency syndrome reference center in Rio de Janeiro, Brazil. *Am J Respir Crit Care Med*. 2000;162(6):2238-40.
- McWilliams T, Wells AU, Harrison AC, Lindstrom S, Cameron RJ, Foskin E. Induced sputum and bronchoscopy in the diagnosis of pulmonary tuberculosis. *Thorax*. 2002;57(12):1010-4.
- Kudoh S, Kudoh T. A simple technique for culturing tubercle bacilli. *Bull World Health Organ*. 1974;51(1):71-82.
- Burrill J, Williams CJ, Bain G, Conder G, Hine AL, Misra RR. Tuberculosis: a radiologic review. *Radiographics*. 2007;27(5):1255-73.
- McAdams HP, Erasmus J, Winter JA. Radiologic manifestations of pulmonary tuberculosis. *Radiol Clin North Am*. 1995;33(4):655-78.

30. Rosemberg J, Tarantino AB, Sobreiro MC. Tuberculose. In: Tarantino AB, editor. Doenças Pulmonares. Rio de Janeiro: Guanabara-Koogan; 2008. p. 266-330.
31. Capone D, Mogami R, Miyagui T. Tomografia computadorizada de alta resolução nas doenças difusas pulmonares – correlação anatomopatológica. São Paulo: Atheneu; 2003.
32. Campos CA, Marchiori E, Rodrigues R. Tuberculose pulmonar: achados na tomografia computadorizada de alta resolução do tórax em pacientes com doença em atividade comprovada bacteriologicamente. *J Pneumol*. 2002;28(1):23-9.
33. Wang YH, Lin AS, Lai YF, Chao TY, Liu JW, Ko SF. The high value of high-resolution computed tomography in predicting the activity of pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2003;7(6):563-8.
34. Siddiqi K, Lambert ML, Walley J. Clinical diagnosis of smear-negative pulmonary tuberculosis in low-income countries: the current evidence. *Lancet Infect Dis*. 2003;3(5):288-96.
35. Conde MB, Loivos AC, Rezende VM, Soares SL, Mello FC, Reingold AL, et al. Yield of sputum induction in the diagnosis of pleural tuberculosis. *Am J Respir Crit Care Med*. 2003;167(5):723-5.
36. Kaisemann MC, Kritski AL, Pereira MF, Trajman A. Pleural fluid adenosine deaminase detection for the diagnosis of pleural tuberculosis. *J Bras Pneumol*. 2004;30(6):549-56.
37. Morisson P, Neves DD. Evaluation of adenosine deaminase in the diagnosis of pleural tuberculosis: a Brazilian meta-analysis. *J Bras Pneumol*. 2008;34(4):217-24.
38. Neves DD, Dias RM, Cunha AJ, Chibante AM. Efficiency of clinical, radiological and laboratory testing in the diagnosis of pleural tuberculosis. *J Bras. Pneumol*. 2004;30(4):319-26.
39. Porcel JM, Alemán C, Bielsa S, Sarrapio J, Fernández de Sevilla T, Esquerda A. A decision tree for differentiating tuberculous from malignant pleural effusions. *Respir Med*. 2008;102(8):1159-64.
40. Feres MC, Martino MC, Maldijian S, Batista F, Gabriel Jr A, Tufik S. Laboratorial validation of an automated assay for the determination of adenosine deaminase activity in pleural fluid and cerebrospinal fluid. *J Bras Pneumol*. 2008;34(12):1033-9.
41. Jiang J, Shi HZ, Liang QL, Qin SM, Qin XJ. Diagnostic value of interferon-gamma in tuberculous pleurisy: a metaanalysis. *Chest*. 2007;131(4):1133-41.
42. Polesky A, Grove W, Bhatia G. Peripheral tuberculous lymphadenitis: epidemiology, diagnosis, treatment, and outcome. *Medicine (Baltimore)*. 2005;84(6):350-62.
43. Daley P, Thomas S, Pai M. Nucleic acid amplification tests for the diagnosis of tuberculous lymphadenitis: a systematic review. *Int J Tuberc Lung Dis*. 2007;11(11):1166-76.
44. Portillo-Gómez L, Murillo-Neri MV, Gaitan-Mesa J, Sosa-Iglesias EG. Nested polymerase chain reaction in the diagnosis of cervical tuberculous lymphadenitis in Mexican children. *Int J Tuberc Lung Dis*. 2008;12(11):1313-9.
45. Bhigjee AI, Padayachee R, Paruk H, Hallwirth-Pillay KD, Marais S, Connolly C. Diagnosis of tuberculous meningitis: clinical and laboratory parameters. *Int J Infect Dis*. 2007;11(4):348-54.
46. Török ME, Nghia HD, Chau TT, Mai NT, Thwaites GE, Stepniowska K, et al. Validation of a diagnostic algorithm for adult tuberculous meningitis. *Am J Trop Med Hyg*. 2007;77(3):555-9.
47. Altintepe L, Tonbul HZ, Ozbek I, Guney I, Odabas AR, Cetinkaya R, et al. Urinary tuberculosis: ten years' experience. *Ren Fail*. 2005;27(6):657-61.
48. Browne RF, Zwiwech C, Torreggiani WC. Imaging of urinary tract infection in the adult. *Eur Radiol*. 2004;14 Suppl 3:E168-83.
49. Wang LJ, Wu CF, Wong YC, Chuang CK, Chu SH, Chen CJ. Imaging findings of urinary tuberculosis on excretory urography and computerized tomography. *J Urol*. 2003;169(2):524-8.
50. Mello FC, Fonseca-Costa J. The utility of molecular biology in the diagnosis of tuberculosis. *J Bras Pneumol*. 2005;31(3):187-9.
51. Palomino JC. Nonconventional and new methods in the diagnosis of tuberculosis: feasibility and applicability in the field. *Eur Respir J*. 2005;26(2):339-50.
52. Flores LL, Pai M, Colford JM Jr, Riley LW. In-house nucleic acid amplification tests for the detection of *Mycobacterium tuberculosis* in sputum specimens: meta-analysis and meta-regression. *BMC Microbiol*. 2005;5:55.
53. Greco S, Rulli M, Girardi E, Piersimoni C, Saltini C. Diagnostic accuracy of in-house PCR for pulmonary tuberculosis in smear-positive patients: meta-analysis and metaregression. *J Clin Microbiol*. 2009;47(3):569-76.
54. Centers for Disease Control and Prevention. Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. *MMWR Morb Mortal Wkly Rep*. 2009;58(1):7-10.
55. Martin A, Panaiotov S, Portaels F, Hoffner S, Palomino JC, Angeby K. The nitrate reductase assay for the rapid detection of isoniazid and rifampicin resistance in *Mycobacterium tuberculosis*: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2008;62(1):56-64.
56. Machado A Jr, Emodi K, Takenami I, Finkmoore BC, Barbosa T, Carvalho J, et al. Analysis of discordance between the tuberculin skin test and the interferon-gamma release assay. *Int J Tuberc Lung Dis*. 2009;13(4):446-53.
57. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med*. 2008;149(3):177-84.
58. Cailleaux-Cezar M, de A Melo D, Xavier GM, de Salles CL, de Mello FC, Ruffino-Netto A, et al. Tuberculosis incidence among contacts of active pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2009;13(2):190-5.
59. Gerald LB, Tang S, Bruce F, Redden D, Kimerling ME, Brook N, et al. A decision tree for tuberculosis contact investigation. *Am J Respir Crit Care Med*. 2002;166(8):1122-7.
60. Jasmer RM, Nahid P, Hopewell PC. Clinical practice. Latent tuberculosis infection. *N Engl J Med*. 2002;347(23):1860-6.
61. Rose CE Jr, Zerbe GO, Lantz SO, Bailey WC. Establishing priority during investigation of tuberculosis contacts. *Am Rev Respir Dis*. 1979;119(4):603-9.
62. Menzies D. Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. *Am J Respir Crit Care Med*. 1999;159(1):15-21.
63. Morrone N, Solha MS. Incidência de tuberculose-doença e de teste tuberculino positivo em crianças expostas a pacientes com tuberculose. Importância dos fatores ligados a fonte e a criança, ate mesmo vacinação prévia com BCG intradérmico. *AMB Rev Assoc Med Bras*. 1983;29(11/12):182-8.
64. Salles CG, Ruffino-Netto A, Lapa-e-Silva JR, Kritski AL, Cailleaux-Cesar M, Queiroz-Mello FC, et al. The presence of a booster phenomenon among contacts of active pulmonary tuberculosis cases: a retrospective cohort. *BMC Public Health*. 2007;7:38.
65. Comstock GW, Baum C, Snider DE Jr. Isoniazid prophylaxis among Alaskan Eskimos: a final report

- of the betheI isoniazid studies. *Am Rev Respir Dis.* 1979;119(5):827-30.
66. Taylor Z, Nolan CM, Blumberg HM; American Thoracic Society; Centers for Disease Control and Prevention; Infectious Diseases Society of America. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2005;54(RR-12):1-81. Erratum in: *MMWR Morb Mortal Wkly Rep.* 2005;54(45):1161.
 67. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. *Am J Respir Crit Care Med.* 2000;161(4 Pt 2):S221-47.
 68. Fountain FF, Tolley E, Chrisman CR, Self TH. Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. *Chest.* 2005;128(1):116-23.
 69. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA.* 1999;281(11):1014-8.
 70. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis.* 2005;40(5):670-6.
 71. Feja K, McNeley E, Tran CS, Burzynski J, Saiman L. Management of pediatric multidrug-resistant tuberculosis and latent tuberculosis infections in New York City from 1995 to 2003. *Pediatr Infect Dis J.* 2008;27(10):907-12.
 72. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207; quiz CE1-4.
 73. Chung WS, Chang YC, Yang MC. Factors influencing the successful treatment of infectious pulmonary tuberculosis. *Int J Tuberc Lung Dis.* 2007;11(1):59-64.
 74. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis – emergency update. Geneva: World Health Organization, Stop TB Department; 2008.
 75. Conde MB, Efron A, Loredo C, De Souza GR, Graça NP, Cezar MC, et al. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. *Lancet.* 2009;373(9670):1183-9.
 76. Mitchison DA. How drug resistance emerges as a result of poor compliance during short course chemotherapy for tuberculosis. *Int J Tuberc Lung Dis.* 1998;2(1):10-5.
 77. Five-year follow-up of a controlled trial of five 6-month regimens of chemotherapy for pulmonary tuberculosis. Hong Kong Chest Service/British Medical Research Council. *Am Rev Respir Dis.* 1987;136(6):1339-42.
 78. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide. Results at 30 months. Hong Kong Chest Service/British Medical Research Council. *Am Rev Respir Dis.* 1991;143(4 Pt 1):700-6.
 79. Combs DL, O'Brien RJ, Geiter LJ. USPHS Tuberculosis Short-Course Chemotherapy Trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med.* 1990;112:397-406.
 80. Mitchison DA. The diagnosis and therapy of tuberculosis during the past 100 years. *Am J Respir Crit Care Med.* 2005;171(7):699-706.
 81. Blomberg B, Fourie B. Fixed-dose combination drugs for tuberculosis: application in standardised treatment regimens. *Drugs.* 2003;63(6):535-53.
 82. World Health Organization. Treatment of tuberculosis: guidelines for national programmes. Geneva: World Health Organization; 2003.
 83. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med.* 2007;120(8):713-9.
 84. Chideya S, Winston CA, Peloquin CA, Bradford WZ, Hopewell PC, Wells CD, et al. Isoniazid, rifampin, ethambutol, and pyrazinamide pharmacokinetics and treatment outcomes among a predominantly HIV-infected cohort of adults with tuberculosis from Botswana. *Clin Infect Dis.* 2009;48(12):1685-94.
 85. Benator D, Bhattacharya M, Bozeman L, Burman W, Cantazaro A, Chaisson R, et al. Rifampentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet.* 2002;360(9332):528-34.
 86. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Programa Nacional de DST e Aids. Recomendações para terapia anti-retroviral em adultos infectados pelo HIV: 2008. Brasília: Ministério da Saúde; 2008.
 87. Apers L, Wijarajah C, Mutsvangwa J, Chigara N, Mason P, van der Stuyft P. Accuracy of routine diagnosis of pulmonary tuberculosis in an area of high HIV prevalence. *Int J Tuberc Lung Dis.* 2004;8(8):945-51.
 88. Churchyard GJ, Scano F, Grant AD, Chaisson RE. Tuberculosis preventive therapy in the era of HIV infection: overview and research priorities. *J Infect Dis.* 2007;196 Suppl 1:S52-62.
 89. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med.* 2006;174(8):935-52.
 90. Golub JE, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, King BS, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS.* 2007;21(11):1441-8.
 91. National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (Centers for Disease Control and Prevention). Division of Tuberculosis Elimination. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. Atlanta: Department of Health and Human Services, Centers for Disease Control and Prevention; 2007.
 92. Snider DE Jr, Layde PM, Johnson MW, Lyle MA. Treatment of tuberculosis during pregnancy. *Am Rev Respir Dis.* 1980;122(1):65-79.
 93. American Thoracic Society; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR Recomm Rep.* 2003;52(RR-11):1-77. Erratum in: *MMWR Recomm Rep.* 2005;53(51):1203. Dosage error in article text.
 94. Morrone N, Marques WJ, Fazolo N, Soares LC, Macedo L. Reações adversas e interações das drogas tuberculostáticas. *J Pneumol.* 1993;19(1):52-9.
 95. World Health Organization. Toman's Tuberculosis: Case detection, treatment, and monitoring – questions and answers. Geneva: World Health Organization; 2004.
 96. Chang KC, Leung CC, Yew WW, Lau TY, Tam CM. Hepatotoxicity of pyrazinamide: cohort and case-

- control analyses. *Am J Respir Crit Care Med.* 2008;177(12):1391-6.
97. Saigal S, Agarwal SR, Nandeesh HP, Sarin SK. Safety of an ofloxacin-based antitubercular regimen for the treatment of tuberculosis in patients with underlying chronic liver disease: a preliminary report. *J Gastroenterol Hepatol.* 2001;16(9):1028-32.
 98. Szklo A, Mello FC, Guerra RL, Dorman SE, Muzy-de-Souza GR, Conde MB. Alternative anti-tuberculosis regimen including ofloxacin for the treatment of patients with hepatic injury. *Int J Tuberc Lung Dis.* 2007;11(7):775-80.
 99. John GT, Shankar V. Mycobacterial infections in organ transplant recipients. *Semin Respir Infect.* 2002;17(4):274-83.
 100. Nuernberger EL, Yoshimatsu T, Tyagi S, O'Brien RJ, Vernon AN, Chaisson RE, et al. Moxifloxacin-containing regimen greatly reduces time to culture conversion in murine tuberculosis. *Am J Respir Crit Care Med.* 2004;169(3):421-6.
 101. Johnson JL, Hadad DJ, Boom WH, Daley CL, Peloquin CA, Eisenach KD, et al. Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis.* 2006;10(6):605-12.
 102. Burman WJ, Goldberg S, Johnson JL, Muzanye G, Engle M, Mosher AW, et al. Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. *Am J Respir Crit Care Med.* 2006;174(3):331-8.
 103. Dewan R, Pratap H. Surgical interventions in multidrug-resistant tuberculosis: Retrospective analysis of 74 patients treated at a tertiary level care center. *Ind J Thorac Cardiovasc Surg.* 2006;22(1):15-8.
 104. Park SK, Lee CM, Heu JP, Song SD. A retrospective study for the outcome of pulmonary resection in 49 patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis.* 2002;6(2):143-9.
 105. Leite LP, Costa AL, Andrade RN, Galvão T. Tratamento cirúrgico adjuvante de tuberculose pulmonar multirresistente. *J Pneumol.* 1997;23(1):11-4.
 106. Shiraishi Y, Nakajima Y, Katsuragi N, Kurai M, Takahashi N. Resectional surgery combined with chemotherapy remains the treatment of choice for multidrug-resistant tuberculosis. *J Thorac Cardiovasc Surg.* 2004;128(4):523-8.
 107. Somocurcio JG, Sotomayor A, Shin S, Portilla S, Valcarcel M, Guerra D, et al. Surgery for patients with drug-resistant tuberculosis: report of 121 cases receiving community-based treatment in Lima, Peru. *Thorax.* 2007;62(5):416-21.
 108. Wang H, Lin H, Jiang G. Pulmonary resection in the treatment of multidrug-resistant tuberculosis: a retrospective study of 56 cases. *Ann Thorac Surg.* 2008;86(5):1640-5.
 109. Kir A, Tahaoğlu K, Okur E, Hatipoğlu T. Role of surgery in multi-drug-resistant tuberculosis: results of 27 cases. *Eur J Cardiothorac Surg.* 1997;12(4):531-4.
 110. Pomerantz BJ, Cleveland JC Jr, Olson HK, Pomerantz M. Pulmonary resection for multi-drug resistant tuberculosis. *J Thorac Cardiovasc Surg.* 2001;121(3):448-53.
 111. Shiraishi Y, Katsuragi N, Kita H, Toishi M, Onda T. Experience with pulmonary resection for extensively drug-resistant tuberculosis. *Interact Cardiovasc Thorac Surg.* 2008;7(6):1075-8.
 112. Park SK, Kim JH, Kang H, Cho JS, Smego RA Jr. Pulmonary resection combined with isoniazid- and rifampin-based drug therapy for patients with multidrug-resistant and extensively drug-resistant tuberculosis. *Int J Infect Dis.* 2009;13(2):170-5.
 113. Mitnick CD, Shin SS, Seung KJ, Rich ML, Atwood SS, Furin JJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. *N Engl J Med.* 2008;359(6):563-74.
 114. Marsico GA, Guimarães CA, Montessi J, Costa AM, Madeira L. Controle da hemoptise maciça com broncoscopia rígida e soro fisiológico gelado. *J Pneumol.* 2003;29(5):280-6.
 115. Rizzi A, Rocco G, Robustellini M, Rossi G, Della Pona C, Massera F. Results of surgical management of tuberculosis: experience in 206 patients undergoing operation. *Ann Thorac Surg.* 1995;59(4):896-900.
 116. Papagiannopoulos KA, Linegar AG, Harris DG, Rossouw GJ. Surgical management of airway obstruction in primary tuberculosis in children. *Ann Thorac Surg.* 1999;68(4):1182-6.
 117. Souilamas R, Riquet M, Barthes FP, Chehab A, Capuani A, Faure E. Surgical treatment of active and sequelar forms of pulmonary tuberculosis. *Ann Thorac Surg.* 2001;71(2):443-7.
 118. Sant'anna CC, Orfalais CT, March Mde F, Conde MB. Evaluation of a proposed diagnostic scoring system for pulmonary tuberculosis in Brazilian children. *Int J Tuberc Lung Dis.* 2006;10(4):463-5.
 119. Marais BJ, Gie RP, Hesseling AC, Schaaf HS, Lombard C, Enarson DA, et al. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. *Pediatrics.* 2006;118(5):e1350-9.
 120. Gie R. Diagnostic atlas of intrathoracic tuberculosis in children: A guide for low income countries. Paris: International Union against Tuberculosis and Lung Disease; 2003.
 121. Pedrozo C, Sant'Anna C, de Fátima March M, Lucena S. Clinical scoring system for paediatric tuberculosis in HIV-infected and non-infected children in Rio de Janeiro. *Int J Tuberc Lung Dis.* 2009;13(3):413-5.
 122. Maciel EL, Dietze R, Lyrio RP, Vinhas SA, Palaci M, Rodrigues RR, et al. Accuracy of inpatient and outpatient gastric lavage in the diagnosis of pulmonary tuberculosis in children. *J Bras Pneumol.* 2008;34(6):404-11.
 123. Hatherill M, Hawkrigde T, Zar HJ, Whitelaw A, Tameris M, Workman L, et al. Induced sputum or gastric lavage for community-based diagnosis of childhood pulmonary tuberculosis? *Arch Dis Child.* 2009;94(3):195-201.
 124. Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet.* 2005;365(9454):130-4.
 125. Alves R, Sant'Anna CC, March MF, Ormonde LR, Cruz KC, Gonçalves CM. Comprovação bacteriológica de tuberculose em crianças como validação de critérios diagnósticos. *Arq Bras Ped.* 1995;2(1):15-21.
 126. Donato L, Helms P, Barats A, Lebris V. Bronchoscopy in childhood pulmonary tuberculosis [Article in French]. *Arch Pediatr.* 2005;12 Suppl 2:S127-31.
 127. Le Roux P, Quinque K, Bonnel AS, Le Luyer B. Extrapulmonary tuberculosis in childhood [Article in French]. *Arch Pediatr.* 2005;12 Suppl 2:S122-6.
 128. Teo HE, Peh WC. Skeletal tuberculosis in children. *Pediatr Radiol.* 2004;34(11):853-60.
 129. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207; quiz CE1-4.
 130. Zampoli M, Kilborn T, Eley B. Tuberculosis during early antiretroviral-induced immune reconstitution

- in HIV-infected children. *Int J Tuberc Lung Dis.* 2007;11(4):417-23.
131. Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet.* 2006;367(9517):1173-80.
 132. Colditz GA, Berkey CS, Mosteller F, Brewer TF, Wilson ME, Burdick E, et al. The efficacy of bacillus Calmette-Guérin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. *Pediatrics.* 1995;96(1 Pt 1):29-35.
 133. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. *Lancet.* 2009;373(9674):1543-9.
 134. Barreto ML, Pereira SM, Ferreira AA. BCG vaccine: efficacy and indications for vaccination and revaccination. *J Pediatr (Rio J).* 2006;82(3 Suppl):S45-54.
 135. Leung CC, Tam CM, Chan SL, Chan-Yeung M, Chan CK, Chang KC. Efficacy of the BCG revaccination programme in a cohort given BCG vaccination at birth in Hong Kong. *Int J Tuberc Lung Dis.* 2001;5(8):717-23.
 136. Rahman M, Sekimoto M, Hira K, Koyama H, Imanaka Y, Fukui T. Is Bacillus Calmette-Guérin revaccination necessary for Japanese children? *Prev Med.* 2002;35(1):70-7.
 137. Rodrigues LC, Pereira SM, Cunha SS, Genser B, Ichihara MY, de Brito SC, et al. Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. *Lancet.* 2005;366(9493):1290-5.
 138. Dantas OM, Ximenes RA, de Albuquerque Mde F, da Silva NL, Montarroyos UR, de Souza WV, et al. A case-control study of protection against tuberculosis by BCG revaccination in Recife, Brazil. *Int J Tuberc Lung Dis.* 2006;10(5):536-41.
 139. Hesseling AC, Marais BJ, Gie RP, Schaaf HS, Fine PE, Godfrey-Faussett P, et al. The risk of disseminated Bacille Calmette-Guérin (BCG) disease in HIV-infected children. *Vaccine.* 2007;25(1):14-8.
 140. Menzies D, Fanning A, Yuan L, Fitzgerald M. Tuberculosis among health care workers. *N Engl J Med.* 1995;332(2):92-8.
 141. Wenger PN, Otten J, Breeden A, Orfas D, Beck-Sague CM, Jarvis WR. Control of nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis* among healthcare workers and HIV-infected patients. *Lancet.* 1995;345(8944):235-40.
 142. Maloney SA, Pearson ML, Gordon MT, Del Castillo R, Boyle JF, Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. *Ann Intern Med.* 1995;122(2):90-5.
 143. Maciel EL, Prado TN, Fávero JL, Moreira TR, Dietze R. Tuberculosis in health professionals: a new perspective on an old problem. *J Bras Pneumol.* 2009;35(1):83-90.
 144. Ferreira MM, Ferrazoli L, Palaci M, Salles PS, Medeiros LA, Novoa P, et al. Tuberculosis and HIV infection among female inmates in São Paulo, Brazil: a prospective cohort study. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1996;13(2):177-83.
 145. Bock N. Tuberculosis Infection Control in the Era of Expanding HIV Care and Treatment Addendum to WHO Guidelines for the Prevention of Tuberculosis in Health Care Facilities in Resource-Limited Settings. Washington: U.S. Dept. of Health and Human Services; 2007.
 146. Bonifacio N, Saito M, Gilman RH, Leung F, Cordova Chavez N, Chacaltana Huarcaya J, et al. High risk for tuberculosis in hospital physicians, Peru. *Emerg Infect Dis.* 2002;8(7):747-8.
 147. Franco C, Zanetta DM. Assessing occupational exposure as risk for tuberculous infection at a teaching hospital in São Paulo, Brazil. *Int J Tuberc Lung Dis.* 2006;10(4):384-9.
 148. Maciel EL, Meireles W, Silva AP, Fiorotti K, Dietze R. Nosocomial *Mycobacterium tuberculosis* transmission among healthcare students in a high incidence region, in Vitória, State of Espírito Santo. *Rev Soc Bras Med Trop.* 2007;40(4):397-9.
 149. de Oliveira HB, Cardoso JC. Tuberculosis among city jail inmates in Campinas, São Paulo, Brazil [Article in Spanish]. *Rev Panam Salud Publica.* 2004;15(3):194-9.
 150. Pazin-Filho A, Soares CS, Ferrais Ada S, Oliveira e Castro Pde T, Bellissimo-Rodrigues F, Nogueira Jde A, et al. Tuberculosis among health care workers in a Brazilian tertiary hospital emergency unit. *Am J Emerg Med.* 2008;26(7):796-8.
 151. do Prado TN, Galavote HS, Brioshi AP, Lacerda T, Fregona G, Detoni Vdo V, et al. Epidemiological profile of tuberculosis cases reported among health care workers at the University Hospital in Vitoria, Brazil. *J Bras Pneumol.* 2008;34(8):607-13.
 152. Joshi R, Reingold AL, Menzies D, Pai M. Tuberculosis among health-care workers in low- and middle-income countries: a systematic review. *PLoS Med.* 2006;3(12):e494.
 153. Roth VR, Garrett DO, Laserson KF, Starling CE, Kritski AL, Medeiros EA, et al. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals. *Int J Tuberc Lung Dis.* 2005;9(12):1335-42.
 154. Granich R. Guidelines for the Prevention of Tuberculosis in Health Care Facilities in Resource-Limited Settings. Geneva: World Health Organization; 1999.
 155. World Health Organization. Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Emergency Update 2008. Geneva: World Health Organization; 2008.
 156. Rothman RE, Hsieh YH, Yang S. Communicable respiratory threats in the ED: tuberculosis, influenza, SARS, and other aerosolized infections. *Emerg Med Clin North Am.* 2006;24(4):989-1017.
 157. Curran ET, Hoffmann PN, Pratt RJ. Tuberculosis and infection control: a review of the evidence. *Br J Infect Control.* 2006;7(2):18-23.
 158. Humphreys H. Control and prevention of healthcare-associated tuberculosis: the role of respiratory isolation and personal respiratory protection. *J Hosp Infect.* 2007;66(1):1-5.
 159. Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. *PLoS Med.* 2007;4(1):e20.
 160. Davies PD, Yew WW, Ganguly D, Davidow AL, Reichman LB, Dheda K, et al. Smoking and tuberculosis: the epidemiological association and immunopathogenesis. *Trans R Soc Trop Med Hyg.* 2006;100(4):291-8.
 161. Güler M, Unsal E, Dursun B, Aydın O, Capan N. Factors influencing sputum smear and culture conversion time among patients with new case pulmonary tuberculosis. *Int J Clin Pract.* 2007;61(2):231-5.
 162. Thomas A, Gopi PG, Santha T, Chandrasekaran V, Subramani R, Selvakumar N, et al. Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India. *Int J Tuberc Lung Dis.* 2005;9(5):556-61.
 163. Mohan CI, Bishai D, Cavalcante S, Chaisson RE. The cost-effectiveness of DOTS in urban Brazil. *Int J Tuberc Lung Dis.* 2007;11(1):27-32.
 164. Brasil. Ministério da Saúde. VIGITEL Brasil 2006 - vigilância de fatores e risco e proteção para doenças crônicas por inquérito telefônico. Brasília: Ministério da Saúde; 2007.