INTERNATIONAL STANDARDS FOR

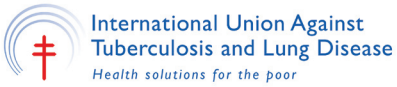
Tuberculosis Care

DIAGNOSIS TREATMENT PUBLIC HEALTH

2ND EDITION, 2009

Developed by the Tuberculosis Coalition for Technical Assistance (TBCTA)

TBCTA Partners:



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ISTC and related materials are posted on www.istcweb.org

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Table of Contents

Acknowledgements

Development of Editions 1 and 2 of the *International Standards for Tuberculosis Care (ISTC)* was supervised by steering committees whose members were chosen to represent perspectives and areas of expertise relevant to tuberculosis care and control. Because of the considerable overlap between the two editions the members of both committees are listed.

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- **Fran Du Melle** (American Thoracic Society) provided administrative coordination as well as guidance on dissemination and implementation.
- **Adriana Deutz** (American Thoracic Society) provided administrative staffing.
- **Kelly Smith** (University of California, San Francisco) managed production of the document.

In addition to the steering committees, many individuals have provided valuable input to one or the other (or both) of the documents. All comments received were given serious consideration by the co-chairs, although not all were incorporated into the document. The following individuals had substantive comments during the process of drafting the *ISTC*. Inclusion of their names does not imply their approval of the final document.

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List of Abbreviations

AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
ATS	American Thoracic Society
BCG	Bacille Calmette-Guérin
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DOT	Directly observed treatment
DOTS	The internationally recommended strategy for tuberculosis control
DR	Drug-resistant
DST	Drug susceptibility testing
EMB	Ethambutol
FDC	Fixed-dose combination
FM	Fluorescence microscopy
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
IDSA	Infectious Diseases Society of America
IGRA	Interferon-gamma release assay
INH	Isoniazid
IMAAI	Integrated Management of Adolescent and Adult Illness
IMCI	Integrated Management of Childhood Illness
IPT	Isoniazid preventive therapy
ISTC	International Standards for Tuberculosis Care
IUATLD	International Union Against Tuberculosis and Lung Disease (The Union)
JATA	Japanese Antituberculosis Association
KNCV	KNCV Tuberculosis Foundation
LTBI	Latent tuberculosis infection
MIC	Minimal inhibitory concentration
MDR	Multidrug-resistant
MSH	Management Sciences for Health
NAAT	Nucleic acid amplification test
NTM	Non-tuberculous mycobacteria
NTP	National tuberculosis control program
PCTC	Patients' Charter for Tuberculosis Care
PPM	Public-private mix
PZA	Pyrazinamide
RIF	Rifampicin
RR	Risk ratio
STI	Sexually transmitted infection
TB	Tuberculosis
TBCTA	Tuberculosis Coalition for Technical Assistance
TST	Tuberculin skin test (Mantoux)
USAID	United States Agency for International Development
WHO	World Health Organization
XDR	Extensively drug-resistant
ZN	Ziehl-Neelsen staining

Preface to Edition 2

It has now been three years since the ISTC was written: new information has emerged; new approaches are now feasible; and new guidelines have been written; these changes warrant an updating of the ISTC.

Development Process

Development of the first edition of the International Standards for Tuberculosis Control (*ISTC*) was funded by the United States Agency for International Development (USAID) via the Tuberculosis Coalition for Technical Assistance (TBCTA) and was guided by a steering committee of 27 members from 14 countries, representing relevant perspectives and areas of expertise. The committee was co-chaired by Mario Raviglione of the World Health Organization (WHO) and Philip Hopewell of the American Thoracic Society (ATS). The group first agreed on a content outline and then identified areas in which systematic reviews were needed. Six questions, largely related to approaches to diagnosis, were identified. Because treatment had been reviewed recently in recommendations developed by the WHO Stop TB Department and by the ATS, Centers for Disease Control and Prevention (CDC), and Infectious Disease Society of America (IDSA), no questions related to treatment were identified. All six of these reviews have now been published in peer-reviewed publications.

The *ISTC* went through 10 drafts with the penultimate draft being circulated for input from a large group of potential users as well as interested parties. The final draft was independently reviewed and approved by the members of the TBCTA, ATS, CDC, the KNCV Tuberculosis Foundation (KNCV), The Union, and WHO. It has subsequently been endorsed by more than 50 national and international organizations and is widely used in tuberculosis control programs globally.

Development of Edition 2 of the ISTC was also funded by USAID via TBCTA. A new steering committee of 50 persons from 15 countries, plus WHO, chaired by Drs. Raviglione and Hopewell guided the process. Committee members were selected to represent relevant perspectives and expertise. The group identified content areas in which revisions were necessary. A list of the changes is shown in Table 1 of the document. Only one systematic review, related to contact investigation (subsequently published), was identified. Edition 2 was circulated for review by potential users and interested parties and has been reviewed and approved by the current TBCTA members (ATS, CDC, Family Health International [FHI], the Japan Antituberculosis Association [JATA], KNCV, Management Sciences for Health [MSH], The Union, and WHO). All steering committee members completed a declaration for the Conflict of Interest; no conflicts were declared. The WHO Guidelines Review Committee examined the final draft and offered comments which were also addressed.

Future revision of this document is likely to be undertaken after 3 to 5 years, predicated upon changes occurring in technology and circumstances.

Key differences between ISTC Edition 1 and Edition 2

Edition 1 (2006) of the *International Standards for Tuberculosis Care* stated, "The *Standards* should be viewed as a living document that will be revised as technology, resources, and circumstances change." It has now been three years since the *ISTC* was written: new information has emerged; new approaches are now feasible; and new guidelines have been written. These changes warrant an updating of the *ISTC* to be consistent with the concept of a "living document."

It was also stated in Edition 1 that, "As written, the *Standards* are presented within a context of what is generally considered to be feasible now or in the near future." There is continued recognition that not all of the standards in this edition can be met in all places at this time. However, given the rapidity of technical advances and deployment of new technologies and approaches, it is anticipated that compliance with the standards will be possible in most places in the near future. It is hoped that having standards that are higher than the minimum necessary will serve to stimulate more rapid improvements in tuberculosis care worldwide.

It must be emphasized that the basic principles that underlie the *ISTC* have not changed. Case detection and curative treatment remain the cornerstones of tuberculosis care and control and the fundamental responsibility of providers to ensure completion of treatment is unchanged. Within these basic principles, however, there have been changes that are of sufficient importance to be incorporated into the *ISTC*. The areas of change that are addressed are summarized in Table 1.

As with the 2006 edition of the *ISTC*, the 2009 edition is written to be consistent with existing international recommendations and is intended to complement, not replace, national and local recommendations.

An important companion document of which the reader should be aware is *The Handbook for Utilizing the International Standards for Tuberculosis Care*. The *Handbook* is based mainly on experiences in countries that began utilizing the *ISTC* soon after it was developed and provided documentation of these experiences. The findings from these pilot countries are summarized briefly in the Introduction and in more detail in Annex 1. The *Handbook* is available at www.istcweb.org. A set of tuberculosis training modules based on the *ISTC* is also available on the same website and are described in Annex 2.

A second companion document, the *Patients' Charter for Tuberculosis Care (PCTC)* was developed in tandem with the *ISTC* and describes patient rights and responsibilities. The *ISTC* and the *PCTC* are mutually reinforcing documents, serving to define expectations from both the provider and the patient perspective. The *PCTC* is also available at www.istcweb.org.

TABLE 1.

Key differences between the 2006 and 2009 editions of the ISTC

Section	Key Differences
Introduction	• Wording has been added to emphasize that a key goal of the *ISTC* is to unify care among all healthcare sectors • A section on utilization of the *ISTC* has been added
Standards for Diagnosis	
In general	• The importance of intensified case finding is emphasized • A table presenting a succinct summary of the evidence base for the various diagnostic tests has been added
Standard 1	• Active case finding using symptom-based assessments in high risk populations is emphasized
Standard 2	• The wording has been changed to recommend collection of at least 2 sputum specimens rather than at least 3 specimens
Standard 3	• The phrase, "—where facilities for culture are available—." has been deleted to emphasize that cultures for mycobacteria are an important part of the diagnostic evaluation for patients with suspected extrapulmonary tuberculosis
Standard 4	• This standard is unchanged
Standard 5	• The phrase, "—where facilities for culture are available—." has been deleted to emphasize that sputum cultures for mycobacteria are an important part of the diagnostic evaluation in patients with negative sputum smears • A new algorithm for evaluating persons suspected of having tuberculosis but who have negative sputum smears has been substituted for the previous algorithm • The role of liquid culture media and line-probe assays for detecting resistance to isoniazid and rifampicin is described • An expanded description of the role of radiography and the importance of quality control for radiography has been added
Standard 6	• This standard has been re-written to be consistent with the WHO document, *Guidance for national tuberculosis programmes on the management of tuberculosis in children*
Standards for Treatment	
Standard 7	• This standard is unchanged
Standard 8	• This standard has been re-written to be consistent with revisions of WHO guidelines
Standard 9	• The importance of a treatment supporter is emphasized • The findings of a systematic review of qualitative research on adherence to tuberculosis treatment are presented
Standard 10	• The standard has been changed to reflect revisions to treatment recommendations by WHO
Standard 11	• The original Standard 14 is now Standard 11. The standard has been changed to indicate the need to assess for drug resistance if the sputum smear is positive at completion of 2-3 months of treatment and with treatment failure or relapse. A table describing risk factors for drug resistance has been added to the text. A section on XDR-TB has been added
Standard 12	• The original Standard 15 is now Standard 12. The standard has been changed to reflect the revised WHO recommendations for programmatic management of DR-TB
Standard 13	• The original Standard 11 is now Standard 13

TABLE 1.

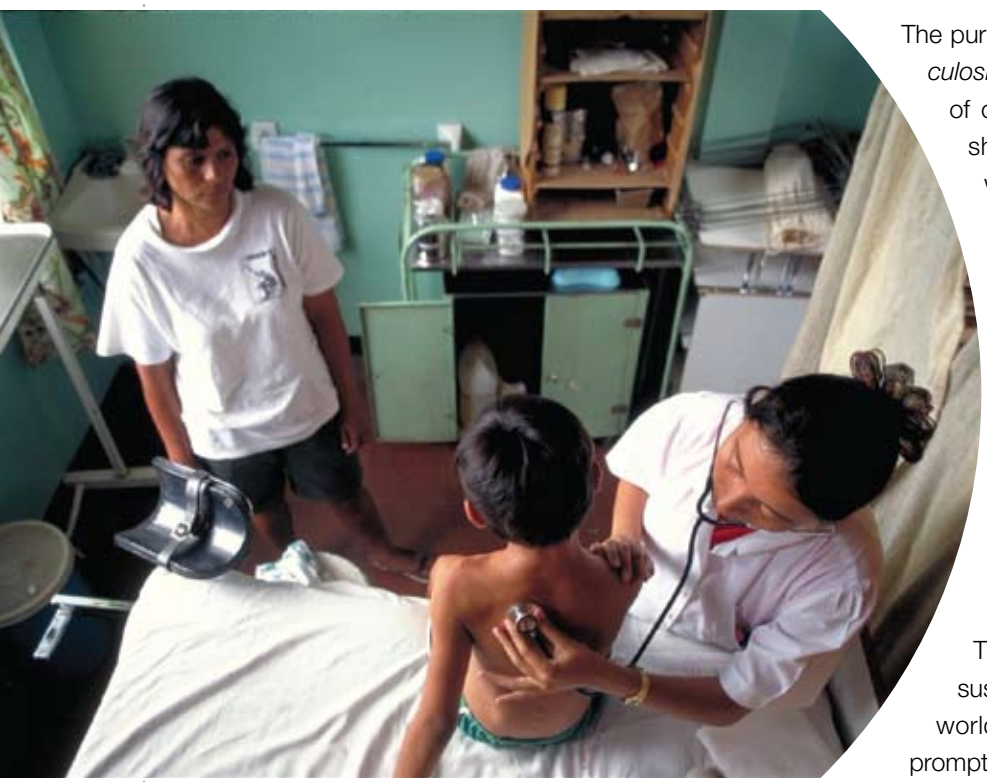
Key differences between the 2006 and 2009 editions of the ISTC

Section	Key Differences
Standards for Addressing HIV Infection and other Co-morbid Conditions	
In general	• This is a new category in the standards
Standard 14	• The original Standard 12 is now Standard 14. It has been rewritten to indicate that all patients with tuberculosis and, in high risk areas or in individuals with risk factors, persons suspected of having tuberculosis should have HIV testing
Standard 15	• The original Standard 13 is now Standard 15
Standard 16	• This is a new standard reflecting recommendations for use of isoniazid preventive therapy in persons with HIV infection
Standard 17	• This is a new standard describing the importance of addressing co-morbid conditions
Standards for Public Health	
Standard 18	• The original Standard 16 is now Standard 18 and has been rewritten to be consistent with current recommendations for contact evaluation and management
Standard 19	• This is a new standard describing the use of isoniazid preventive therapy in children and persons with HIV infection who are contacts of an infectious case
Standard 20	• This is a new standard describing the need for infection control in healthcare facilities
Standard 21	• The original Standard 17 is now Standard 21 and is unchanged

XDR-TB = extensively drug-resistant tuberculosis; **DR-TB** = drug-resistant tuberculosis

As part of the package of *ISTC* materials, a set of tuberculosis training modules based on the standards has been created. The *ISTC Tuberculosis Training Modules* are a comprehensive, flexible, and locally adaptable series of presentations for the training of healthcare providers at all levels. The modules and accompanying trainer's notes and facilitator's guide comprise a tool that can assist in training and educational activities conducted by NTPs, professional societies, medical schools, and other relevant organizations. Since their original release in 2008, the training materials have been fully revised to incorporate the new *ISTC* revisions and new topics have been added. For a full listing of the *ISTC Tuberculosis Training Modules (2009)* refer to Annex 2.

Summary



The purpose of the *International Standards for Tuberculosis Care* is to describe a widely accepted level of care that all practitioners, public and private, should seek to achieve in managing patients who have, or are suspected of having, tuberculosis. The standards are intended to facilitate the effective engagement of all care providers in delivering high quality care for patients of all ages, including those with sputum smear-positive and sputum smear-negative tuberculosis, extrapulmonary tuberculosis, tuberculosis caused by drug-resistant (DR) *Mycobacterium tuberculosis* complex (*M. tuberculosis*) organisms, and tuberculosis combined with HIV infection and other co-morbidities.

The Standards are intended to facilitate the effective engagement of all care providers in delivering high quality care for patients of all ages and all forms of TB including drug-resistant TB and TB combined with HIV infection and other co-morbidities.

The basic principles of care for persons with, or suspected of having, tuberculosis are the same worldwide: a diagnosis should be established promptly and accurately; standardized treatment regimens of proven efficacy should be used, together with appropriate treatment support and supervision; the response to treatment should be monitored; and the essential public health responsibilities must be carried out. Prompt, accurate diagnosis and effective treatment are not only essential for good patient care, they are the key elements in the public health response to tuberculosis and are the cornerstone of tuberculosis control. Thus, all providers who undertake evaluation and treatment of patients with tuberculosis must recognize that, not only are they delivering care to an individual, they are assuming an important public health function that entails a high level of responsibility to the community, as well as to the individual patient.

Although government program providers are not exempt from adherence to the standards in the *ISTC*, non-program providers are the main target audience. It should be emphasized, however, that national and local tuberculosis control programs may need to develop policies and procedures that enable non-program providers to adhere to the *ISTC*. Such accommodations may be necessary, for example, to facilitate treatment supervision and contact investigations, as described in the *ISTC*.

In addition to healthcare providers and government tuberculosis programs, both patients and communities are part of the intended audience. Patients are increasingly aware of and expect that their care will measure up to a high standard. Having generally agreed upon standards will empower patients to evaluate the quality of care they are being provided. Good care for individuals with tuberculosis is also in the best interest of the community.

The standards in the *ISTC* are intended to be complementary to local and national tuberculosis control policies that are consistent with World Health Organization recommendations. They are not intended to replace local guidelines and were written to accommodate local differences in practice. They focus on the contribution that good clinical care of indi-

vidual patients with or suspected of having tuberculosis makes to population-based tuberculosis control. A balanced approach emphasizing both individual patient care and public health principles of disease control is essential to reduce the suffering and economic losses from tuberculosis.

The *ISTC* should be viewed as a living document that will be revised as technology, resources, and circumstances change. As written, the standards in the *ISTC* are presented within a context of what is generally considered to be feasible now or in the near future.

The *ISTC* is also intended to serve as a companion to and support for the *Patients' Charter for Tuberculosis Care (PCTC)*. The *PCTC* specifies patients' rights and responsibilities and will serve as a set of standards from the point of view of the patient, defining what the patient should expect from the provider and what the provider should expect from the patient.

Standards for Diagnosis

Standard 1. All persons with otherwise unexplained productive cough lasting two-three weeks or more should be evaluated for tuberculosis.

Standard 2. All patients (adults, adolescents, and children who are capable of producing sputum) suspected of having pulmonary tuberculosis should have at least two sputum specimens submitted for microscopic examination in a quality-assured laboratory. When possible, at least one early morning specimen should be obtained.

Standard 3. For all patients (adults, adolescents, and children) suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy, culture, and histopathological examination.

Standard 4. All persons with chest radiographic findings suggestive of tuberculosis should have sputum specimens submitted for microbiological examination.

Standard 5. The diagnosis of sputum smear-negative pulmonary tuberculosis should be based on the following criteria: at least two negative sputum smears (including at least one early morning specimen); chest radiographic findings consistent with tuberculosis; and lack of response to a trial of broad-spectrum antimicrobial agents. (Note: Because the fluoroquinolones are active against *M. tuberculosis* complex and, thus, may cause transient improvement in persons with tuberculosis, they should be avoided.) For such patients, sputum cultures should be obtained. In persons who are seriously ill or have known or suspected HIV infection, the diagnostic evaluation should be expedited and if clinical evidence strongly suggests tuberculosis, a course of antituberculosis treatment should be initiated.

Standard 6. In all children suspected of having intrathoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis, bacteriological confirmation should be sought through examination of sputum (by expectoration, gas-

tric washings, or induced sputum) for smear microscopy and culture. In the event of negative bacteriological results, a diagnosis of tuberculosis should be based on the presence of abnormalities consistent with tuberculosis on chest radiography, a history of exposure to an infectious case, evidence of tuberculosis infection (positive tuberculin skin test or interferon-gamma release assay), and clinical findings suggestive of tuberculosis. For children suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy and for culture and histopathological examination.

Standards for Treatment

Standard 7. Any practitioner treating a patient for tuberculosis is assuming an important public health responsibility to prevent ongoing transmission of the infection and the development of drug resistance. To fulfill this responsibility the practitioner must not only prescribe an appropriate regimen, but also utilize local public health services and other agencies, when necessary, to assess the adherence of the patient and to address poor adherence when it occurs.

Standard 8. All patients (including those with HIV infection) who have not been treated previously should receive an internationally accepted first-line treatment regimen using drugs of known bioavailability. The initial phase should consist of two months of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB). The continuation phase should consist of isoniazid and rifampicin given for four months. The doses of antituberculosis drugs used should conform to international recommendations. Fixed dose combinations (FDCs) of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide) and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs are highly recommended.

Standard 9. To assess and foster adherence, a patient-centered approach to administration of drug treatment, based on the patient's needs and mutual respect between the patient and the provider, should be developed for all patients. Supervision and support should be individualized and should draw on the full range of recommended interventions and available support services, including patient counseling and education. A central element of the patient-centered strategy is the use of measures to assess and promote adherence to the treatment regimen and to address poor adherence when it occurs. These measures should be tailored to the individual patient's circumstances and be mutually acceptable to the patient and the provider. Such measures may include direct observation of medication ingestion (directly observed treatment or DOT) and identification and training of a treatment supporter (for tuberculosis and, if appropriate, for HIV) who is acceptable and accountable to the patient and to the health system. Appropriate incentives and enablers, including financial support, may also serve to enhance treatment adherence.

Standard 10. Response to therapy in patients with pulmonary tuberculosis should be monitored by follow-up sputum microscopy (two specimens) at the time of completion of the initial phase of treatment (two months). If the sputum smear is positive at completion of the initial phase, sputum smears should be examined again at 3 months and, if positive, culture and drug susceptibility testing should be performed. In patients with extrapulmonary tuberculosis and in children, the response to treatment is best assessed clinically.

Standard 11. An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance, should be obtained for all patients. Drug susceptibility testing should be performed at the start of therapy for all previously treated patients. Patients who remain sputum smear-positive at completion of 3 months of treatment and patients who have failed, defaulted from, or relapsed following one or more courses of treatment should always be assessed for drug resistance. For patients in whom drug resistance is considered to be likely (see Table 8), culture and testing for susceptibility/resistance to at least isoniazid and rifampicin should be performed promptly. Patient counseling and education should begin immediately to minimize the potential for transmission. Infection control measures appropriate to the setting should be applied.

Standard 12. Patients with or highly likely to have tuberculosis caused by drug-resistant (especially MDR/XDR) organisms should be treated with specialized regimens containing second-line antituberculosis drugs. The regimen chosen may be standardized or based on suspected or confirmed drug susceptibility patterns. At least four drugs to which the organisms are known or presumed to be susceptible, including an injectable agent, should be used and treatment should be given for at least 18–24 months beyond culture conversion. Patient-centered measures, including observation of treatment, are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR/XDR tuberculosis should be obtained.

Standard 13. A written record of all medications given, bacteriologic response, and adverse reactions should be maintained for all patients.

Standards for Addressing HIV Infection and other Co-morbid Conditions

Standard 14. HIV testing and counseling should be recommended to all patients with, or suspected of having, tuberculosis. Testing is of special importance as part of routine management of all patients in areas with a high prevalence of HIV infection in the general population, in patients with symptoms and/or signs of HIV-related conditions, and in patients having a history suggestive of high risk of HIV exposure. Because of the close relationship of tuberculosis and HIV infection, in areas of high HIV prevalence integrated approaches to prevention and treatment of both infections are recommended.

Standard 15. All patients with tuberculosis and HIV infection should be evaluated to determine if antiretroviral therapy is indicated during the course of treatment for tuberculosis. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. However, initiation of treatment for tuberculosis should not be delayed. Patients with tuberculosis and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.

Standard 16. Persons with HIV infection who, after careful evaluation, do not have active tuberculosis should be treated for presumed latent tuberculosis infection with isoniazid for 6-9 months.

Standard 17. All providers should conduct a thorough assessment for co-morbid conditions that could affect tuberculosis treatment response or outcome. At the time the treatment plan is developed, the provider should identify additional services that would support an optimal outcome for each patient and incorporate these services into an individualized plan of care. This plan should include assessment of and referrals for treatment of other illnesses with particular attention to those known to affect treatment outcome, for instance care for diabetes mellitus, drug and alcohol treatment programs, tobacco smoking cessation programs, and other psychosocial support services, or to such services as antenatal or well baby care.

Standards for Public Health

Standard 18. All providers of care for patients with tuberculosis should ensure that persons who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. The determination of priorities for contact investigation is based on the likelihood that a contact: 1) has undiagnosed tuberculosis; 2) is at high risk of developing tuberculosis if infected; 3) is at risk of having severe tuberculosis if the disease develops; and 4) is at high risk of having been infected by the index case. The highest priority contacts for evaluation are:

- Persons with symptoms suggestive of tuberculosis
- Children aged <5 years

- Contacts with known or suspected immunocompromise, particularly HIV infection
- Contacts of patients with MDR/XDR tuberculosis

Other close contacts are a lower priority group.

Standard 19. Children <5 years of age and persons of any age with HIV infection who are close contacts of an infectious index patient and who, after careful evaluation, do not have active tuberculosis, should be treated for presumed latent tuberculosis infection with isoniazid.

Standard 20. Each healthcare facility caring for patients who have, or are suspected of having, infectious tuberculosis should develop and implement an appropriate tuberculosis infection control plan.

Standard 21. All providers must report both new and re-treatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.

Introduction

Purpose

The fundamental purpose of the *International Standards for Tuberculosis Care* is to describe a widely accepted level of care that all practitioners, public and private, should seek to achieve in managing patients who have, or are suspected of having, tuberculosis. The Standards are intended to facilitate the effective engagement of all care providers in delivering high quality care, utilizing established best practices for patients of all ages, including those with smear-positive and smear-negative pulmonary tuberculosis, extrapulmonary tuberculosis, tuberculosis caused by drug-resistant *Mycobacterium tuberculosis* complex (*M. tuberculosis*) organisms, and tuberculosis combined with HIV infection, as well as with other co-morbid conditions. Engagement of all providers is a critical component of the Global Stop TB Strategy, the internationally recommended, comprehensive approach to tuberculosis control worldwide.[1] The Stop TB Strategy presents the strategic framework necessary for effective tuberculosis care and control and, when fully implemented, provides the elements essential for delivery of good tuberculosis care.

A high standard of care is essential to restore the health of individuals with tuberculosis, to prevent the disease in their families and others with whom they come into contact, and to protect the health of communities.

A high standard of care is essential to restore the health of individuals with tuberculosis, to prevent the disease in their families and others with whom they come into contact, and to protect the health of communities.[2] Sub-standard care will result in poor patient outcomes, continued infectiousness with transmission of *M. tuberculosis* to family and other community members, and generation and propagation of drug resistance. For these reasons sub-standard care is not acceptable.[3,4]

In addition to the fundamental purpose of the *ISTC*, important goals are to promote unified approaches to the diagnosis and management of tuberculosis among all categories of clinicians and to facilitate coordination of activities and collaboration between tuberculosis control programs and non-program providers. Given that public health authorities are responsible for normative functions, surveillance, monitoring, evaluation and reporting, it is crucial that there be coordination between control programs and non-program providers, especially in dealing with complicated issues such as diagnosis and management of patients with drug-resistant tuberculosis. The *ISTC* provides a common ground of understanding on which to build collaborations at national, regional, or local levels, or even within individual institutions.

The standards in this document differ from existing guidelines in that the standards present **what** should be done, whereas, guidelines describe **how** the action is to be accomplished. Standards provide the foundation on which care can be based; guidelines provide the framing for the whole structure of care. A standard does not provide specific guidance on disease management but, rather, presents a principle or set of principles that can be applied in nearly all situations. In addition, a standard can be used as an indicator of the overall adequacy of disease management against which individual or collective practices can be measured. Guidelines are systematically developed evidence-based

statements that assist providers, recipients, and other stakeholders to make informed decisions about appropriate health interventions. Health interventions are defined broadly to include not only clinical procedures but also public health actions.[5] Guidelines and standards are, thus, complementary to one another.

The basic principles of care for persons with, or suspected of having, tuberculosis are the same worldwide: a diagnosis should be established promptly and accurately; standardized treatment regimens of proven efficacy should be used, together with appropriate treatment support and supervision; the response to treatment should be monitored; and the essential public health responsibilities must be carried out. The ways in which these principles are applied vary depending on available technology and resources. However, prompt, accurate diagnosis and effective treatment are not only essential for good patient care, they are the key elements in the public health response to tuberculosis and are the cornerstone of tuberculosis control. Thus, all providers who undertake evaluation and treatment of patients with tuberculosis must recognize that, not only are they delivering care to an individual, they are assuming an important public health function that entails a high level of responsibility to the community, as well as to the individual patient. Adherence to the standards in this document will enable these responsibilities to be fulfilled.

Engagement of all providers is a critical component of the Global Stop TB Strategy, the internationally recommended, comprehensive approach to tuberculosis control worldwide.

Audience

The *ISTC* is addressed to all healthcare providers, private and public, who care for persons with proven tuberculosis or with symptoms and signs suggestive of tuberculosis. In general, providers in government tuberculosis programs that follow existing international guidelines are in compliance with the *ISTC*. However, in many instances (as described later under Rationale) clinicians (both private and public) who are not part of a tuberculosis control program lack the guidance and systematic evaluation of outcomes provided by government control programs and, commonly, would not be in compliance with the *ISTC*. Thus, although government program providers are not exempt from adherence to the *ISTC*, non-program providers are the main target audience. It should be emphasized, however, that public tuberculosis control programs may need to develop policies and procedures that enable non-program providers to adhere to the *ISTC*. Such accommodations may be necessary, for example, to facilitate treatment supervision and contact investigations.[6,7]

In addition to healthcare providers and government tuberculosis programs, both patients and communities are part of the intended audience. Patients are increasingly aware of and expect that their care will measure up to a high standard, as described in the *Patients' Charter for Tuberculosis Care*. Having generally agreed upon standards will empower patients to evaluate the quality of care they are being provided. Good care for individuals with tuberculosis is also in the best interest of the community. Community contributions to tuberculosis care and control are increasingly important in raising public awareness of the disease, providing treatment support, encouraging adherence, reducing the stigma associated with having tuberculosis, and demanding that healthcare providers in the community adhere to a high standard of tuberculosis care.[8] The community should expect that care for tuberculosis will be up to the accepted standard.

The ISTC is intended to be complementary to local and national tuberculosis control policies that are consistent with World Health Organization (WHO) recommendations and are not intended to replace local guidelines.

Scope

Three main categories of activities are addressed by the *ISTC*: diagnosis, treatment, and public health and prevention. In addition, standards addressing co-morbid conditions are presented. The *ISTC* is intended to be complementary to local and national tuberculosis control policies that are consistent with World Health Organization recommendations. They are not intended to replace local guidelines and were written to accommodate local differences in practice and to be one of a group of available documents that serve to foster a high standard of practice. They focus on the contribution that good clinical care of individual patients with or suspected of having tuberculosis and appropriate prevention measures make to population-based tuberculosis control. A balanced approach emphasizing both individual patient care and public health principles of disease control is essential to reduce the suffering and economic losses from tuberculosis.

To meet the requirements of the *ISTC*, approaches and strategies determined by local circumstances and practices and developed in collaboration with local and national public health authorities, will be necessary. There are many situations in which the level of care can, and should, go beyond what is specified in the *ISTC*. Local conditions, practices, and resources also will determine the degree to which this is the case.

The *ISTC* should be viewed as a living document that will be revised as technology, resources, and circumstances change. As written, the standards are presented within a context of what is generally considered to be feasible now or in the near future. Within the standards priorities may be set that will foster appropriate incremental changes. For example, rather than expecting full implementation of all diagnostic elements at once, priorities should be set based on local circumstances and capabilities. Pursuing this example, once high quality sputum smear microscopy is universally available the first priority activity to be accomplished would be performing sputum cultures for persons suspected of having tuberculosis but who have negative sputum smears, especially those in areas of high HIV prevalence. The second priority would consist of obtaining cultures or other microbiological tests to confirm the diagnosis and to determine drug susceptibility for patients at high risk of having tuberculosis caused by drug-resistant organisms. A third priority would be performing cultures for all persons suspected of having tuberculosis. In some settings, as a fourth priority, testing for drug susceptibility/resistance should be performed for isolates of *M. tuberculosis* obtained from patients not responding to standardized treatment regimens and, finally, for initial isolates from all patients.

The *ISTC* is also intended to serve as a companion to and support for the *PCTC*. The *PCTC* specifies patients' rights and responsibilities and serves as a set of standards from the point of view of the patient, defining what the patient should expect from the provider and what the provider should expect from the patient.

There are several critical areas that the *ISTC* does not address. Their exclusion should not be regarded as an indication of their lack of importance, but, rather, their being beyond the scope of this document. The *ISTC* does not address the extremely important concern with overall access to care. Obviously, if there is no care available, the quality of care is not relevant. Additionally, there are many factors that impede access even when care is available: poverty, gender, stigma, and geography are prominent among the factors that inter-

fere with persons seeking or receiving care. Also, if the residents of a given area perceive that the quality of care provided by the local facilities is sub-standard, they will not seek care there. This perception of quality is a component of access that adherence to these standards will address.[2]

Also not addressed by the *ISTC* is the necessity of having a sound, effective government tuberculosis control program. The standards in the *ISTC* cannot be achieved without there being an enabling environment, generally provided by an effective government program supported by appropriate legal and regulatory framework and financial resources. The requirements of such programs to ensure effective treatment are described in a number of international recommendations from the WHO, the CDC, and The Union.[9-11] Having an effective control program at the national or local level with linkages to non-program providers enables bidirectional communication of information including case notification, consultation, patient referral, provision of drugs or services such as treatment supervision/support for private patients, and contact evaluation. In addition the program may be the only source of laboratory services for the private sector.

In providing care for patients with, or suspected of having, tuberculosis, clinicians and persons responsible for healthcare facilities should take measures that reduce the potential for transmission of *M. tuberculosis* to healthcare workers and to other patients by following local, national, or international guidelines for infection control. This is especially true in areas or specific populations with a high prevalence of HIV infection. Detailed recommendations are contained in the WHO document, *Guidelines for Prevention of Tuberculosis in Health Care Facilities in Resource-Limited Settings*,[12] and the updated CDC guidelines for preventing the transmission of *M. tuberculosis* in healthcare settings.[13]

Rationale

Although in the past decade there has been substantial progress in the development and implementation of the strategies necessary for effective tuberculosis control, the disease remains an enormous global health problem.[14-18] One-third of the world's population is infected with *M. tuberculosis*, mostly in developing countries where 95% of cases occur.[15] In 2008, there were an estimated 9.3 million new cases of tuberculosis, of which 4.1 million were sputum smear-positive and, thus, highly infectious.[18] The number of tuberculosis cases that occur in the world each year has been essentially unchanged for the past few years, although the global case rate per 100,000 population now shows a slight decrease. Case rates are now decreasing in all six of the WHO regions. In Africa the case rate has only recently begun to decrease but remains very high both because of the epidemic of HIV infection in sub-Saharan countries and the poor health systems and primary care services throughout the region.[14-16,18] In Eastern Europe after a decade of increases, case rates reached a plateau in the early 2000's and now have begun to decrease slightly. The increases in the 1990's are attributable to the collapse of the public health infrastructure, increased poverty, and other socioeconomic factors complicated further by the high prevalence of drug-resistant tuberculosis.[18,19] In many countries, because of incomplete application of effective care and control measures, tuberculosis case rates are either stagnant or decreasing more slowly than should be expected. This is especially true in high risk groups such as persons with HIV infection, the homeless, and recent immigrants. The

failure to bring about a more rapid reduction in tuberculosis incidence, at least in part, relates to a failure to fully engage non-tuberculosis control program providers in the provision of high quality care, in coordination with local and national control programs. Fostering such engagement is an important purpose of the *ISTC*.[20]

It is widely recognized that many providers are involved in the diagnosis and treatment of tuberculosis.[21-24] Traditional healers, general and specialist physicians, nurses, clinical officers, academic physicians, unlicensed practitioners, physicians in private practice, practitioners of alternative medicine, and community organizations, among others, all play roles in tuberculosis care and, therefore, in tuberculosis control. In addition, other public providers, such as those working in prisons, army hospitals or public hospitals and facilities, regularly evaluate persons suspected of having tuberculosis and treat patients who have the disease.

Any person anywhere in the world who is unable to access quality health care should be considered vulnerable to tuberculosis and its consequences.

Little is known about the adequacy of care delivered by non-program providers, but evidence from studies conducted in many different parts of the world show great variability in the quality of tuberculosis care, and poor quality care continues to plague global tuberculosis control efforts.[18] A global situation assessment reported by WHO suggested that delays in diagnosis were common.[23] The delay was more often in receiving a diagnosis rather than in seeking care, although both elements have been shown to be important.[25,26] The WHO survey and other studies also show that clinicians, in particular those who work in the private healthcare sector, often deviate from standard, internationally recommended, tuberculosis management practices.[22,23] These deviations include under-utilization of sputum smear microscopy for diagnosis, generally associated with over-reliance on radiography; use of non-recommended drug regimens with incorrect combinations of drugs and mistakes in both drug dosage and duration of treatment; and failure to supervise and assure adherence to treatment.[22,23,26-32] Anecdotal evidence also suggests over-reliance on poorly validated or inappropriate diagnostic tests such as serologic assays, often in preference to conventional bacteriological evaluations.

Together, these findings highlight flaws in healthcare practices that lead to sub-standard tuberculosis care for populations that, sadly, are most vulnerable to the disease and are least able to bear the consequences of such systemic failures. Any person anywhere in the world who is unable to access quality health care should be considered vulnerable to tuberculosis and its consequences.[2] Likewise, any community with no or inadequate access to appropriate diagnostic and treatment services for tuberculosis is a vulnerable community.[2] The development of the *ISTC* is an attempt to reduce vulnerability of individuals and communities to tuberculosis by promoting high-quality care for persons with, or suspected of having, tuberculosis.

Utilization of the ISTC

The *ISTC* is potentially a very powerful tool to improve the quality of tuberculosis care. Because of the way in which the *ISTC* was developed and the international endorsements it has received, the document is broadly credible across categories of practitioners. This credibility is a major strength of the *ISTC* and should be capitalized upon in its utilization.

Ideally, the *ISTC* should be used in conjunction with three other documents: the *Tool for National Situation Assessment*[33] developed by the WHO and the Stop TB Partnership; *Engaging all Health Care Providers in TB Control*[34] developed by the WHO; and the *Patients' Charter for Tuberculosis Care (PCTC)*. The first of these documents presents a framework for analyzing the role of all sectors in providing tuberculosis care and control; the second presents guidance on implementing public-private mix (PPM) approaches; the third specifies the rights and responsibilities of patients (www.worldcarecouncil.org), was developed in tandem with the *ISTC*. Taken together, the framework and guidance can be used to develop a tailored, comprehensive multi-sectoral approach to tuberculosis care and control at the local or national level, with each component having a set of defined roles and responsibilities.

A variety of possible ways in which the *ISTC* could be utilized is summarized in Annex 1.

Companion and Reference Documents

The *ISTC* is complementary to five important companion documents. The first is the *PCTC*, noted above. Second, the International Council of Nurses has developed a set of standards, *TB/MDR-TB Nursing Standards* (www.icn.ch/tb/standards.htm), that define in detail the critical roles and responsibilities of nurses in the care and control of tuberculosis. Third, The Union developed a nursing guide that describes best nursing practices for tuberculosis care and control.[35] Fourth, as a single-source reference for many of the practices for tuberculosis care, we refer the reader to *Toman's Tuberculosis: Case Detection, Treatment, and Monitoring. (second edition).*[36] Fifth, the revised *TB Handbook (Implementing the Stop TB strategy: a handbook for national tuberculosis control programmes)*[37] serves as a general reference for implementation of the Stop TB strategy.

There are many guidelines and recommendations on various aspects of tuberculosis care and control. The *ISTC* draws from many of these documents to provide its evidence base. In particular we have relied on guidelines that are generally accepted because of the process by which they were developed and by their broad use. However, existing guidelines, although implicitly based on standards, do not present standards that define the acceptable level of care in such a way as to enable assessment of the adequacy of care by patients themselves, by communities, and by public health authorities.

In providing the evidence base for the *ISTC*, generally, we have cited summaries, meta-analyses, and systematic reviews of evidence that have examined and synthesized primary data, rather than referring to the primary data itself. Throughout the document we have used the terminology recommended in the *Revised International Definitions in Tuberculosis Control.*[38]

Standards for Diagnosis

Not all patients with respiratory symptoms receive an adequate evaluation for tuberculosis. These failures result in missed opportunities for earlier detection of tuberculosis and lead to increased disease severity for the patients and a greater likelihood of transmission of M. tuberculosis to family members and others in the community.

Early and accurate diagnosis is critical to tuberculosis care and control. There is substantial evidence that failure to identify cases early is a major weak link in efforts to control the disease, resulting in ongoing transmission in the community and in more severe, progressive disease in the affected person.[39] Although sputum (or other specimen) smear microscopy remains the most widely available test to establish a microbiological diagnosis, other more sensitive means of identifying *M. tuberculosis* are rapidly gaining acceptance as their performance and applicability are increasingly understood.[40] However, it must be emphasized that the major delays in diagnosing tuberculosis result from the patient not seeking care and/or the provider not suspecting the disease, rather than technological limitations.[39] While improving the performance of diagnostic tests is important, improving patients' and providers' awareness of the disease and their understanding of approaches to diagnosis is at least equally important.

Table 2 presents a succinct summary of the evidence base for the various diagnostic tests mentioned.[41]

TABLE 2.

Findings from systematic reviews on tuberculosis (TB) diagnostic tests*

Diagnostic test (references)	Major findings/results of systematic reviews
Diagnosis of Pulmonary Tuberculosis	
Sputum smear microscopy[42-44]	• Fluorescence microscopy is on average 10% more sensitive than conventional microscopy. Specificity of both fluorescence and conventional microscopy is similar • Centrifugation and overnight sedimentation, preceded with any of several chemical methods (including bleach) is more sensitive than direct microscopy; specificity is unaffected by sputum processing methods • When serial sputum specimens are examined, the mean incremental yield and/or increase in sensitivity from examination of 3rd sputum specimen ranges between 2% to 5%
Nucleic acid amplification tests (NAATs) [40,45-52]	NAATs have high specificity and positive predictive value. NAATs, however, have relatively lower (and highly variable) sensitivity and negative predictive value for all forms of TB, especially in smear-negative and extrapulmonary disease. In-house ("home brew") NAATs produce highly inconsistent results as compared to commercial, standardized NAATs
Commercial serological antibody detection tests [52-54]	Serological tests for both pulmonary and extrapulmonary TB produce highly inconsistent estimates of sensitivity and specificity; none of the assays perform well enough to replace microscopy
Automated liquid cultures [52]	Automated liquid cultures are more sensitive than solid cultures; time to detection is more rapid than solid cultures
Diagnosis of Latent Tuberculosis Infection	
Tuberculin skin test (TST, Mantoux)[55,56]	• Individuals who had received BCG vaccination are more likely to have a positive TST; the effect of BCG on TST results is less after 15 years; positive TST with indurations of >15 mm are more likely to be the result of TB infection than of BCG vaccination • The effect on TST of BCG received in infancy is minimal, especially 10 years after vaccination. BCG received after infancy produces more frequent, more persistent, and larger TST reactions. Non-tuberculous mycobacterial (NTM) infection is not a clinically important cause of false-positive TST, except in populations with a high prevalence of NTM sensitization and a very low prevalence of TB infection
T-cell-based interferon-gamma release assays (IGRAs)[57-59]	IGRAs have excellent specificity (higher than the tuberculin skin test, especially for BCG vaccinated persons) and are unaffected by prior BCG vaccination
Diagnosis of Drug Resistance	
Line probe assays: INNO-LiPA Rif. TB [LiPA] [60] and GenoType MTBDR assays[61]	• LiPA is a highly sensitive and specific test for the detection of rifampicin resistance in culture isolates. The test has relatively lower sensitivity when used directly on clinical specimens • The GenoType MTBDR assays have excellent sensitivity and specificity for rifampicin and isoniazid resistance even when directly used on clinical specimens
Colorimetric redox-indicator methods[62] and nitrate reductase assays[63]	Colorimetric methods and nitrate reductase assays are highly sensitive and specific for the rapid detection of rifampicin and isoniazid resistance in culture isolates

* Source: This table has been modified with the author's permission from Pai M, Ramsay A, O'Brien R. Evidence-based tuberculosis diagnosis. PLoS Med. 2008;5: e156.

STANDARD 1. All persons with otherwise unexplained productive cough lasting two-three weeks or more should be evaluated for tuberculosis.

Rationale and Evidence Summary

The most common symptom of pulmonary tuberculosis is persistent cough productive of mucus and sometimes blood (hemoptysis). In persons with tuberculosis the cough is often accompanied by systemic symptoms, such as fever, night sweats, and weight loss. In addition, findings, such as lymphadenopathy, consistent with concurrent extrapulmonary tuberculosis, may be noted, especially in patients with HIV infection. Active case finding using accurate symptom-based assessments to identify persons who should be evaluated for tuberculosis is especially important in areas where there is a high prevalence of the disease and in settings where high risk populations and susceptible individuals, such as persons with HIV infection congregate.[64]

Although most patients with pulmonary tuberculosis have cough, the symptom is not specific to tuberculosis; it can occur in a wide range of respiratory conditions, including acute respiratory tract infections, asthma, and chronic obstructive pulmonary disease. Having cough of 2-3 weeks duration serves as the criterion for defining suspected tuberculosis and is used in most national and international guidelines, particularly in areas of moderate to high prevalence of tuberculosis as an indication to initiate an evaluation for the disease.[9,11,36,38,65] In a survey conducted in primary health care services of 9 low- and middle-income countries with a low prevalence of HIV infection, respiratory complaints, including cough, constituted on average 18.4% of symptoms that prompted a visit to a health center for persons older than 5 years of age. Of this group, 5% of patients overall were categorized as possibly having tuberculosis because of the presence of an unexplained cough for more than 2–3 weeks.[66] Other studies have shown that 4–10% of adults attending outpatient health facilities in developing countries may have a persistent cough of more than 2–3 weeks duration.[67] This percentage varies somewhat depending on whether there is pro-active questioning concerning the presence of cough. Respiratory conditions, therefore, constitute a substantial proportion of the burden of diseases in patients presenting to primary healthcare services.[66,67]

Data from India, Algeria, and Chile generally show that the percentage of patients with positive sputum smears increases with increasing duration of cough from 1–2 weeks, increasing to 3–4, and >4 weeks.[68] However, in these studies even patients with shorter duration of cough had an appreciable prevalence of tuberculosis. A more recent assessment from India demonstrated that by using a threshold of >2 weeks to prompt collection of sputum specimens, the number of patients with suspected tuberculosis increased by 61% but, more importantly, the number of tuberculosis cases identified increased by 46% compared with a threshold of >3 weeks.[69] The results also suggested that actively inquiring as to the presence of cough in all adult clinic attendees may increase the yield of cases; 15% of patients who, without prompting, volunteered that they had cough, had positive smears, but, in addition, 7% of patients who did not volunteer that they had cough but, on questioning, admitted to having cough >2 weeks had positive smears.[69]

Choosing a threshold of 2–3 weeks is an obvious compromise, and it should be recognized that, while using this threshold reduces the clinic and laboratory workload, some cases would be missed. In patients presenting with chronic cough, the proportion of

cases attributable to tuberculosis will depend on the prevalence of tuberculosis in the community.[67] In countries with a low prevalence of tuberculosis, it is likely that chronic cough will be due to conditions other than tuberculosis. Conversely, in high prevalence countries, tuberculosis will be one of the leading diagnoses to consider, together with other conditions, such as asthma, bronchitis, and bronchiectasis that are common in many areas.

Overall, by focusing on adults and children presenting with persistent cough, the chances of identifying patients with pulmonary tuberculosis are maximized. Unfortunately, several studies suggest that not all patients with respiratory symptoms receive an adequate evaluation for tuberculosis.[23,26,28-31,70] These failures result in missed opportunities for earlier detection of tuberculosis and lead to increased disease severity for the patients and a greater likelihood of transmission of *M. tuberculosis* to family members and others in the community.

STANDARD 2. All patients (adults, adolescents, and children who are capable of producing sputum) suspected of having pulmonary tuberculosis should have at least two sputum specimens submitted for microscopic examination in a quality-assured laboratory. When possible, at least one early morning specimen should be obtained.

Rationale and Evidence Summary

To establish a diagnosis of tuberculosis every effort must be made to identify the causative agent of the disease. A microbiological diagnosis can only be confirmed by culturing *M. tuberculosis* complex or identifying specific nucleic acid sequences in a specimen from any suspected site of tuberculosis. In practice, however, there are many resource-limited settings in which culture or other methods of identification are not available currently. Fortunately, microscopic examination of stained sputum is feasible in nearly all settings, and the diagnosis of tuberculosis can be strongly inferred by finding acid-fast bacilli (AFB) by microscopic examination. In nearly all clinical circumstances in high prevalence areas, finding acid-fast bacilli in stained sputum is highly specific and, thus, is the equivalent of a confirmed diagnosis. In addition to being highly specific for *M. tuberculosis* complex, identification of acid-fast bacilli by microscopic examination is particularly important for three reasons: it is the most rapid method for determining if a person has tuberculosis; it identifies persons who are at greatest risk of dying from the disease*; and it identifies the most likely transmitters of infection.

Generally, it is the responsibility of government health systems (national tuberculosis control programs [NTPs] or others) to ensure that providers and patients have convenient access to microscopy laboratories. It is crucial that all laboratories, public and private, undergo assessments of quality and have programs for quality improvement. These qual-

* It should be noted that in persons with HIV infection, mortality rates are greater in patients with clinically-diagnosed tuberculosis who have negative sputum smears than among HIV-infected patients who have positive sputum smears. [71-74]

ity assessments are generally the responsibility of a government system (usually the NTP) or other certifying agencies.

Failure to perform a proper diagnostic evaluation before initiating treatment for tuberculosis potentially exposes the patient to the risks of unnecessary or wrong treatment with no benefit. Moreover, such an approach may delay accurate diagnosis and proper treatment. This standard applies to adults, adolescents, and children. With proper instruction and supervision many children five years of age and older can generate a specimen. Adolescents, although often classified as children at least until the age of 15 years, can generally produce sputum. Thus, age alone is not sufficient justification for failing to attempt to obtain a sputum specimen from a child or adolescent.

Failure to perform a proper diagnostic evaluation before initiating treatment for tuberculosis potentially exposes the patient to the risks of unnecessary or wrong treatment with no benefit. Moreover, such an approach may delay accurate diagnosis and proper treatment.

The information summarized below describes the results of various approaches to sputum collection, processing, and examination. The application of the information to actual practices and policies should be guided by local considerations.

The optimum number of sputum specimens to establish a diagnosis has been examined in a number of studies that have served to support recommendations.[74] In a rigorously conducted systematic review of 37 studies on this topic, it was found that, on average, the initial specimen was positive in 85.8% of all patients ultimately found to have acid-fast bacilli detected, in an additional 11.9% with the second specimen, and a further 2.3% on the third specimen.[39] In studies that used culture as the reference standard, the mean incremental yield in sensitivity of the second specimen was 11.1% and that of the third was 3.1%.

A re-analysis of data from a study involving 42 laboratories in four high-burden countries showed that the incremental yield from a third sequential specimen ranged from 0.7% to 7.2%.[75] Thus, it appears that in a diagnostic evaluation for tuberculosis, at least two specimens should be obtained. In some settings, because of practicality and logistics, a third specimen may be useful, but examination of more than two specimens adds minimally to the number of positive specimens obtained.[44] Ideally, the results of sputum microscopy should be returned to the clinician within no more than one working day from submission of the specimen. The timing of specimen collection is also important. The yield appears to be greatest from early morning (overnight) specimens.[44,76-78] Thus, although it is not practical to collect only early morning specimens, at least one early morning specimen should be obtained. Early detection of patients with infectious tuberculosis is an important component of infection control in healthcare facilities, thus, sputum specimens should be collected promptly from patients suspected of having the disease and laboratories should quickly return the results.

A variety of methods have been used to improve the performance of sputum smear microscopy.[43,44,79] In general, the sensitivity of microscopy (as compared with culture) is higher with concentration by centrifugation and/or sedimentation (usually after pre-treatment with chemicals such as bleach, sodium hydroxide [NaOH], and N-acetyl L-cysteine [NALC] or both) as compared to direct (unconcentrated) smear microscopy. A comprehensive systematic review of 83 studies describing the effects of various physical and/or chemical methods for concentrating and processing sputum prior to microscopy found that concentration resulted in a higher sensitivity (15–20% increase) and smear-positivity rate, when compared with direct smears.[43] Although there are demonstrable advantages

to concentration of sputum, there are also disadvantages. Centrifugation is more complex, requires electrical power, and may be associated with increased infection risk to laboratory personnel. Consequently, it is not clear that the advantages offset the disadvantages in low-resource settings.

Fluorescence microscopy (FM), in which auramine-based staining causes the acid-fast bacilli to fluoresce against a dark background, is widely used in many parts of the world. A comprehensive systematic review of 45 studies, in which the performance of direct sputum smear microscopy using fluorescence staining was compared with Ziehl-Neelsen (ZN) staining using culture as the gold standard, suggests that FM is the more sensitive method.[42] This review showed that FM is on average 10% more sensitive than conventional light microscopy. The specificity of FM was comparable to Ziehl-Neelsen microscopy. The combination of increased sensitivity with little or no loss of specificity makes FM a more accurate test, although the increased cost and complexity has restricted its use in many areas. For this reason conventional FM has best been used in centers with specifically trained and proficient microscopists, in which a large number of specimens are processed daily, and in which there is an appropriate quality control program. However, it is anticipated that lower cost, light emitting diode (LED) fluorescence microscopes with performance characteristics superior to conventional that are now available will be widely implemented.

STANDARD 3. For all patients (adults, adolescents, and children) suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy, culture, and histopathological examination.

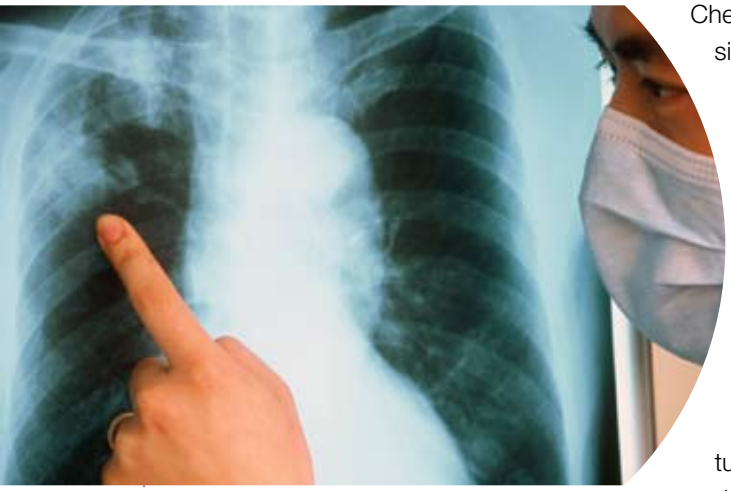
Rationale and Evidence Summary

Extrapulmonary tuberculosis (without associated lung involvement) accounts for 15–20% of tuberculosis in populations with a low prevalence of HIV infection. In populations with a high prevalence of HIV infection, the proportion of cases with extrapulmonary tuberculosis is higher. Because appropriate specimens may be difficult to obtain from some of these sites, bacteriological confirmation of extrapulmonary tuberculosis is often more difficult than for pulmonary tuberculosis. In spite of the difficulties, however, the basic principle that bacteriological confirmation of the diagnosis should be sought still holds. Generally, there are fewer *M. tuberculosis* organisms present in extrapulmonary sites so identification of acid-fast bacilli by microscopy in specimens from these sites is less frequent and culture is more important. For example, microscopic examination of pleural fluid in tuberculous pleuritis detects acid-fast bacilli in only about 5–10% of cases, and the diagnostic yield is similarly low in tuberculous meningitis. Given the low yield of microscopy, both culture and histopathological examination of tissue specimens, such as may be obtained by needle biopsy of lymph nodes, are important diagnostic tests. In addition to the collection of specimens from the sites of suspected tuberculosis, examination of sputum and a chest radiograph may also be useful, especially in patients with HIV infection, in whom there is an appreciable frequency of subclinical pulmonary tuberculosis.[80]

In patients who have an illness compatible with tuberculosis that is severe or progressing rapidly, initiation of treatment should not be delayed pending the results of microbiological examinations. Treatment should be started while awaiting results and then modified if necessary based on the microbiological findings.

STANDARD 4. All persons with chest radiographic findings suggestive of tuberculosis should have sputum specimens submitted for microbiological examination.

Rationale and Evidence Summary



Chest radiography is a sensitive but nonspecific test to detect tuberculosis.[81] Radiographic examination (film, digital imaging, or fluoroscopy) of the thorax or other suspected sites of involvement may be useful to identify persons for further evaluation. However, a diagnosis of tuberculosis cannot be established by radiography alone. Reliance on the chest radiograph as the only diagnostic test for tuberculosis will result in both over-diagnosis of tuberculosis and missed diagnoses of tuberculosis and other diseases. As summarized, in a study from India in which 2,229 outpatients were examined by photofluorography, 227 were classified as having tuberculosis by radiographic criteria.[82,83] Of the 227, 81 (36%) had negative sputum cultures, whereas, of the remaining 2,002 patients 31 (1.5%) had positive cultures. Looking at these results in terms of the sensitivity of chest radiography 31 (18%) of 177 culture positive cases would have been missed by radiography. Given these and other data, it is clear that the use of radiographic examinations alone to diagnose tuberculosis is not an acceptable practice.

Reliance on the chest radiograph as the only diagnostic test for tuberculosis will result in both over-diagnosis of tuberculosis and missed diagnoses of tuberculosis and other diseases.

Chest radiography is useful to evaluate persons who have negative sputum smears to attempt to find evidence for pulmonary tuberculosis and to identify other abnormalities that may be responsible for the symptoms. With regard to tuberculosis, radiographic examination is most useful when applied as part of a systematic approach in the evaluation of persons whose symptoms and/or findings suggest tuberculosis, but who have negative sputum smears. (See Standard 5.)

STANDARD 5. **The diagnosis of sputum smear-negative pulmonary tuberculosis should be based on the following criteria: at least two negative sputum smears (including at least one early morning specimen); chest radiographic findings consistent with tuberculosis; and lack of response to a trial of broad-spectrum antimicrobial agents. (Note: Because the fluoroquinolones are active against *M. tuberculosis* complex and, thus, may cause transient improvement in persons with tuberculosis, they should be avoided.) For such patients, sputum cultures should be obtained. In persons who are seriously ill or have known or suspected HIV infection, the diagnostic evaluation should be expedited and if clinical evidence strongly suggests tuberculosis, antituberculosis treatment should be initiated.**

Rationale and Evidence Summary

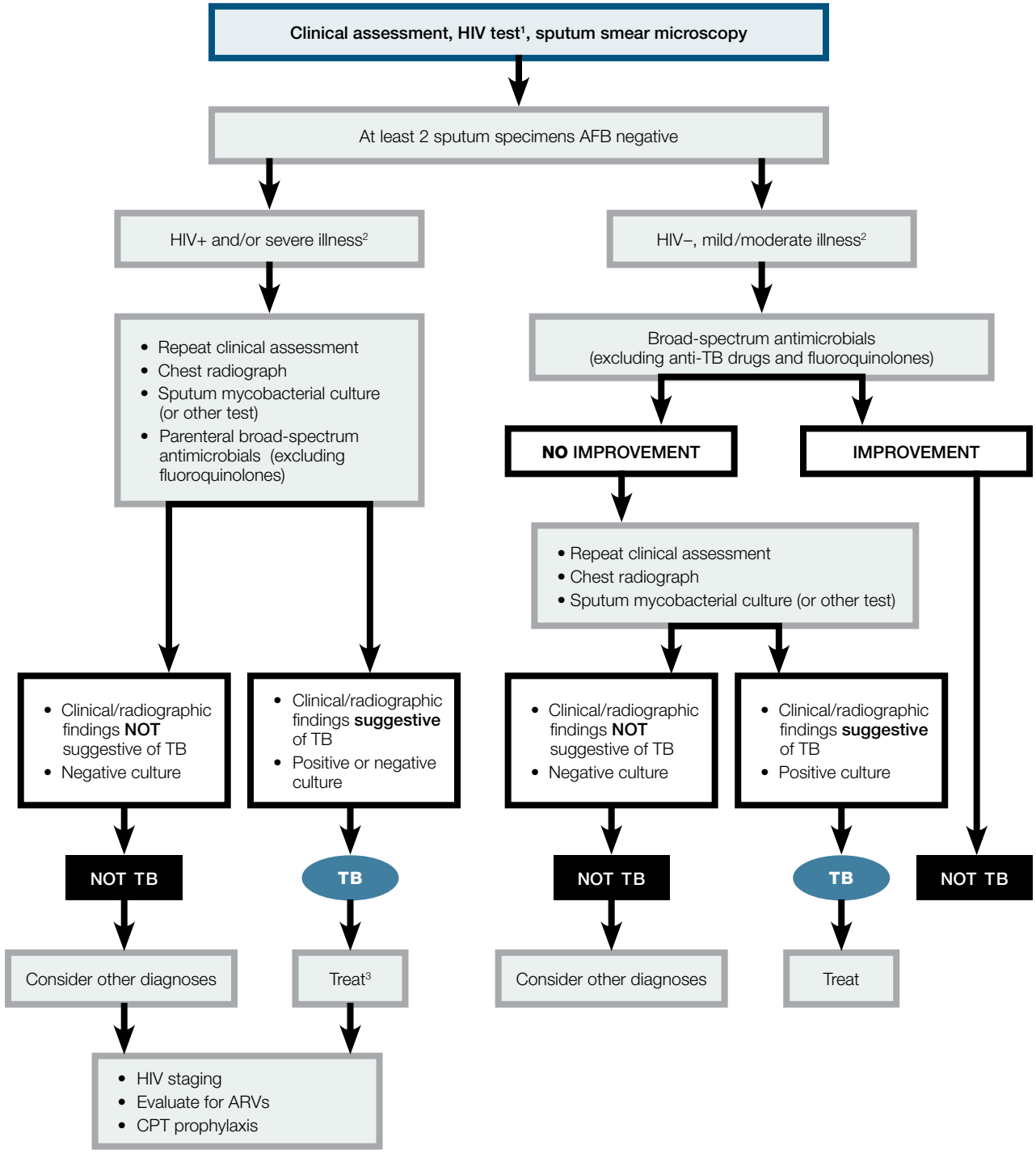
The designation of "sputum smear-negative tuberculosis" presents a difficult diagnostic dilemma. On average, sputum smear microscopy is only about 50–60% sensitive when compared with culture. Nevertheless, given the nonspecific nature of the symptoms of tuberculosis and the multiplicity of other diseases that could be the cause of the patient's illness, it is important that a rigorous approach be taken in diagnosing tuberculosis in a patient in whom at least two adequate sputum specimens are negative by microscopy. Because patients with HIV infection and tuberculosis frequently have negative sputum smears, and because of the broad differential diagnosis, including *Pneumocystis jiroveci* pneumonia, and bacterial and fungal lower respiratory infections, in this group such a systematic approach to diagnosis is crucial. It is important, however, to balance the need for a systematic approach, in order to avoid both over- and under-diagnosis of tuberculosis, with the need for prompt treatment in a patient with an illness that is progressing rapidly. Over-diagnosis of tuberculosis when the illness has another cause will delay proper diagnosis and treatment, whereas, under-diagnosis will lead to more severe consequences of tuberculosis, including disability and possibly death, as well as ongoing transmission of *M. tuberculosis*. It should be noted that in making a diagnosis based on the above three criteria, a clinician who decides to treat with a full course of antituberculosis chemotherapy should report this as a case of sputum smear-negative pulmonary tuberculosis to local public health authorities (as described in Standard 21).

A number of algorithms have been developed as a means to systematize the diagnosis of smear-negative tuberculosis, although none has been adequately validated under field conditions.[84-86] In particular, there is little information or experience on which to base approaches to the diagnosis of smear-negative tuberculosis in persons with HIV infection when culture is not routinely available. Figure 1 is a composite algorithm modified from algorithms developed by WHO.[9,37,65,86] It is included as an example of a systematic approach. It should be recognized that, commonly, the steps in the algorithm are not followed in a sequential fashion but may be done concurrently or in parallel with, for example, chest radiography, an antimicrobial trial, and collection of sputum specimens for culture all done at the same time. The algorithm should be viewed as presenting an approach to diagnosis that incorporates the main components of and a framework for the diagnostic evaluation.

There are several points of caution regarding the algorithm. First, completion of all of the steps requires a substantial amount of time; thus, it should not be used for patients with

FIGURE 1.

An illustrative approach to the diagnosis of sputum smear-negative pulmonary tuberculosis



AFB = acid-fast bacilli; **TB** = tuberculosis; **ARVs** = antiretroviral drugs; **CPT** = Cotrimoxazole

1. Recommended in countries or areas with adult HIV prevalence >1% or prevalence among TB cases >5%
2. Severe illness = respiratory rate >30 breaths/min, temperature >39ºC, pulse >120 beats/min, unable to walk unaided, symptoms/signs progressing rapidly
3. In patients with severe illness empiric treatment for TB may be initiated prior to confirmation of diagnosis

an illness that is worsening rapidly. This is especially true in patients with HIV infection in whom tuberculosis and other infections may be rapidly progressive. Second, several studies have shown that patients with tuberculosis may respond, at least transiently, to broad spectrum antimicrobial treatment.[87-89] Obviously such a response will lead one to delay a diagnosis of tuberculosis. Fluoroquinolones, in particular, are bactericidal for *M. tuberculosis* complex. Empiric fluoroquinolone monotherapy for respiratory tract infections has been associated with delays in initiation of appropriate antituberculosis therapy and acquired resistance to the fluoroquinolones.[90] Third, the approach outlined in the algorithm may be costly to the patient and deter the patient from continuing with the diagnostic evaluation. Given all these concerns, application of such an algorithm in patients with at least two negative sputum specimen examinations must be done in a flexible manner. Ideally, the evaluation of smear-negative tuberculosis should be guided by locally-validated approaches, suited to local conditions, and the needs (financial or otherwise) of the patient.

Although sputum smear microscopy is the first bacteriologic test of choice, culture should be included in the algorithm for evaluating patients with negative sputum smears. Properly done, culture adds a significant layer of complexity and cost but also increases sensitivity, which should result in earlier case detection.[91,92] Although the results of culture may not be available until after a decision to begin treatment has to be made, treatment can be stopped subsequently if cultures from a reliable laboratory are negative, the patient has not responded clinically, and the clinician has sought other evidence in pursuing the differential diagnosis. It must be emphasized that, for seriously ill patients (particularly patients with HIV infection), a clinical decision to start treatment often must be made without waiting for the results of cultures. Such patients may die if appropriate treatment is not begun promptly.

Although sputum smear microscopy is the first bacteriologic test of choice, culture adds a significant layer of complexity and cost but also increases sensitivity, which should result in earlier case detection.

The probability of finding acid-fast bacilli in sputum smears by microscopy is directly related to the concentration of bacilli in the sputum. Sputum microscopy is likely to be positive when there are at least 10,000 organisms per milliliter of sputum. At concentrations below 1,000 organisms per milliliter of sputum, the chance of observing acid-fast bacilli in a smear is less than 10%.[93,94] In contrast, a properly performed culture can detect far lower numbers of acid-fast bacilli (detection limit is about 100 organisms per ml).[92] The culture, therefore, has a higher sensitivity than microscopy and, at least in theory, can increase case detection, although this potential has not been demonstrated in low-income, high-incidence areas. Further, culture makes it possible to identify the mycobacterial species and to perform drug susceptibility testing in patients in whom there is reason to suspect drug-resistant tuberculosis.[92] The disadvantages of culture are its cost, technical complexity and the time required to obtain a result, thereby imposing a diagnostic delay if there is less reliance on sputum smear microscopy. In addition, ongoing quality assessment is essential for culture results to be credible. Such quality assurance measures are not available widely in most low-resource settings.

In many countries, although culture facilities are not uniformly available, there is the capacity to perform culture in some areas. Providers should be aware of the local capacity and use the resources appropriately, especially for the evaluation of persons suspected of

having tuberculosis who have negative sputum smears and for persons suspected of having tuberculosis caused by drug-resistant organisms.

Traditional culture methods use solid media such as Lowenstein-Jensen and Ogawa. Cultures on solid media are less technology-intensive and the media can be made locally. However, the time to identify growth is significantly longer than in liquid media. Liquid media systems such as BACTEC® utilize the release of radioactive CO_2 from C-14 labeled palmitic acid in the media to identify growth. The MGIT® system, also using liquid medium, has the advantage of having growth detected by the appearance of fluorescence in a silicon plug at the bottom of the tube, thereby avoiding radioactivity. Decisions to provide culture facilities for diagnosing tuberculosis depend on financial resources, trained personnel, and the ready availability of reagents and equipment service.

There is good evidence that liquid cultures are more sensitive and rapid than solid media cultures.[41] WHO recently issued policy guidance on the use of liquid media for culture and drug susceptibility testing in low-resource settings. This policy recommends phased implementation of liquid culture systems as a part of a country-specific comprehensive plan for laboratory capacity strengthening that addresses issues such as biosafety, training, maintenance of infrastructure, and reporting of results. However, development of the capacity to do cultures requires a well-functioning healthcare system, adequate laboratory infrastructure, and trained personnel.

In June 2008, WHO endorsed the use of molecular line-probe assays for rapid screening of patients at risk of MDR-TB (www.who.int/tb/en/). This policy statement was based in part on evidence summarized in systematic reviews,[41] expert opinion, and results of field demonstration projects. The recommended use of line probe assays is currently limited to culture isolates and direct testing of smear-positive sputum specimens. Line probe assays are not recommended as a complete replacement for conventional culture and drug susceptibility testing. Culture is still required for smear-negative specimens, and conventional drug susceptibility testing is still necessary to confirm resistance to drugs other than isoniazid and rifampicin.

Nucleic acid amplification tests, although widely distributed, do not offer major advantages over culture at this time, especially in cases of smear-negative tuberculosis because NAATs have a low sensitivity in smear-negative specimens. Although a positive result can be obtained more quickly than with any of the culture methods, the NAATs are not sufficiently sensitive for a negative result to exclude tuberculosis.[40,49,51,95-97] In addition, NAATs are not sufficiently sensitive to be useful in identifying *M. tuberculosis* in specimens from extrapulmonary sites of disease.[46,47,96,97] Moreover, cultures must be available if conventional drug susceptibility testing is to be performed. Other approaches to establishing a diagnosis of tuberculosis, such as serological tests, are not of proven value and should not be used in routine practice at this time.[53,98]

As described in the algorithm, chest radiography also plays an important role in the evaluation of persons suspected of having tuberculosis but who have negative sputum smears. Cough is a nonspecific symptom: the chest radiograph can assist in determining the cause of the cough in persons with negative sputum smear microscopy. Commonly, in areas where radiographic facilities are available the chest radiograph is obtained before sputum examinations and finding an abnormality should prompt the ordering of sputum

specimens. Although the radiograph is a useful adjunct in diagnosing tuberculosis, as noted above, the radiograph cannot establish a diagnosis alone. However, in combination with clinical assessment, the radiograph may provide important circumstantial evidence as to the diagnosis.[99]

It is important to note that, just as with the microbiology laboratory, radiography requires quality control to ensure that the information provided is accurate. Commonly, little attention is paid to the issue of the quality of radiographic examinations, both in terms of their technical quality and the interpretation. As applied to the diagnosis of tuberculosis, poor imaging quality may be more harmful to patients than not having the patients subjected to radiographic examination at all. There are several resources that are useful both for assuring technical quality.[99-101]

STANDARD 6. **In all children suspected of having intrathoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis, bacteriological confirmation should be sought through examination of sputum (by expectoration, gastric washings, or induced sputum) for smear microscopy and culture. In the event of negative bacteriological results, a diagnosis of tuberculosis should be based on the presence of abnormalities consistent with tuberculosis on chest radiography, a history of exposure to an infectious case, evidence of tuberculosis infection (positive tuberculin skin test or interferon-gamma release assay), and clinical findings suggestive of tuberculosis. For children suspected of having extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy and for culture and histopathological examination.**

Rationale and Evidence Summary

The diagnosis of tuberculosis in children relies on careful and thorough assessment of all the evidence derived from the medical history, clinical examination, tuberculin skin test result (or the result of an interferon-gamma release assay), chest radiography, and microbiological evaluation.[102] Although most children with tuberculosis have pulmonary involvement, they commonly have paucibacillary disease without evident lung cavitation but with involvement of intrathoracic lymph nodes. Consequently, compared with adults, sputum smears from children are more likely to be negative. Although bacteriological confirmation is not always feasible, it should be sought whenever possible by sputum smear microscopy and culture for children with suspected pulmonary tuberculosis who are old enough to produce a sputum sample. Because many children less than five years of age do not cough and produce sputum effectively, culture of gastric washings obtained by naso-gastric tube lavage or induced sputum has a higher yield than spontaneous sputum.[103] A trial of treatment with antituberculosis medications is not recommended as a method to diagnose tuberculosis in children. The decision to treat a child should be carefully considered and once such a decision is made, the child should be treated with a full course of therapy.

The diagnosis of tuberculosis in children relies on careful and thorough assessment of all the evidence.

As a component of evaluating a child for tuberculosis, the social situation must be taken into account and the need for support services assessed. The parent or responsible adult must be informed as to the importance of treatment in order to be an effective treatment supporter.

The recommended approach to diagnose tuberculosis in children (summarized in Table 3) is based on limited published evidence and rests heavily on expert opinion.

Several reviews have examined the effectiveness of various diagnostic tools, scoring systems, and algorithms to diagnose tuberculosis in children.[102-106] Many of these approaches lack standardization and validation, and, thus, are of limited applicability. Table 4 presents the approach recommended by the Integrated Management of Childhood Illness (IMCI) program of WHO which is widely used in first-level facilities in low- and middle-income countries.[107]

TABLE 3.

Recommended approach to the diagnosis of tuberculosis in children[102]

1. Careful history (including history of TB contact and symptoms consistent with TB)
2. Clinical examination (including growth assessment)
3. Tuberculin skin testing (or interferon-gamma release assay)
4. Bacteriological evaluation
5. Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB

Source: Modified from: World Health Organization. *Guidance for national tuberculosis programmes on the management of tuberculosis in children*, WHO/HTM/TB/2006.371.[102]

TABLE 4.

Clinical features that suggest the diagnosis of tuberculosis in children[107]

The risk of tuberculosis is increased when there is an active case (infectious, smear-positive tuberculosis) in the same house, or when the child is malnourished, is HIV-infected, or has had measles in the past few months. Tuberculosis should be considered in any child with:

A history of:

- Unexplained weight loss or failure to grow normally
- Unexplained fever, especially when it continues for more than 2 weeks
- Chronic cough
- Exposure to an adult with probable or definite pulmonary infectious tuberculosis

On examination:

- Fluid on one side of the chest (reduced air entry, dullness to percussion)
- Enlarged non-tender lymph nodes or a lymph node abscess, especially in the neck
- Signs of meningitis, especially when these develop over several days and the spinal fluid contains mostly lymphocytes and elevated protein
- Abdominal swelling, with or without palpable lumps
- Progressive swelling or deformity in the bone or a joint, including the spine

Source: Reproduced from *Management of the child with a serious infection or severe malnutrition: Guidelines for care at the first-referral level in developing countries*. Geneva: World Health Organization, 2000. WHO/FCH/CAH/00.1.[107]

Standards for Treatment

Treatment for tuberculosis is not only a matter of individual health—it is also a matter of public health. Thus, all providers, public and private, who undertake to treat a patient with tuberculosis, must have the knowledge to prescribe a standard treatment regimen and the means to assess adherence to the regimen and address poor adherence to ensure that treatment is completed.

STANDARD 7. Any practitioner treating a patient for tuberculosis is assuming an important public health responsibility to prevent ongoing transmission of the infection and the development of drug resistance. To fulfill this responsibility the practitioner must not only prescribe an appropriate regimen, but also utilize local public health services and other agencies, when necessary, to assess the adherence of the patient and to address poor adherence when it occurs.

Rationale and Evidence Summary

As described in the Introduction, the main interventions to prevent the spread of tuberculosis in the community are the detection of patients with infectious tuberculosis and providing them with effective treatment to ensure a rapid and lasting cure. Consequently, treatment for tuberculosis is not only a matter of individual health, as is the case with, for example, treatment of hypertension or diabetes mellitus, it is also a matter of public health. Thus, all providers, public and private, who undertake to treat a patient with tuberculosis, must have the knowledge to prescribe a standard treatment regimen and the means to assess adherence to the regimen and address poor adherence to ensure that treatment is completed.[10] National and local tuberculosis programs commonly possess approaches and tools, including incentives and enablers to ensure adherence with treatment and, when properly organized, can offer these to non-program providers. Failure of a provider to ensure adherence could be equated with, for example, failure to ensure that a child receives the full set of immunizations. Communities and patients deserve to be assured that providers treating tuberculosis are doing so in accordance with this principle and are, thereby, meeting this standard.

STANDARD 8. **All patients (including those with HIV infection) who have not been treated previously should receive an internationally accepted first-line treatment regimen using drugs of known bioavailability. The initial phase should consist of two months of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB). The continuation phase should consist of isoniazid and rifampicin given for four months. The doses of antituberculosis drugs used should conform to international recommendations. Fixed dose combinations (FDCs) of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide) and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs are highly recommended.**

Rationale and Evidence Summary

A large number of well-designed clinical trials have provided the evidence base for this standard and several sets of treatment recommendations based on these studies have been written in the past few years.[9-11,65] All these data indicate that a rifampicin-containing regimen is the backbone of antituberculosis chemotherapy and is highly effective in treating tuberculosis caused by drug-susceptible *M. tuberculosis*. It is also clear from these studies that the minimum duration of treatment for smear and/or culture-positive tuberculosis is six months. For the six-month treatment duration to be maximally effective, the regimen must include pyrazinamide during the initial two-month phase and rifampicin must be included throughout the full six months. There are several variations in the frequency of drug administration, that have been shown to produce acceptable results.[9-11,65]

Two systematic reviews of regimens of less than six months, have found that shorter durations of treatment have an unacceptably high rate of relapse.[108,109] Thus, the current international standard duration of treatment for tuberculosis is a minimum of six months.[9-11,65]

A retrospective review of the outcomes of treatment of tuberculosis in patients with HIV infection showed that relapse is minimized by the use of a regimen containing rifampicin throughout a six-month course of treatment.[110] Moreover, a recent systematic review of the outcome of treatment in the presence of single or poly-drug resistance (not multidrug resistance) demonstrated that failure, relapse, and acquisition of additional resistance were associated with shorter duration of rifampicin therapy.[111]

Intermittent administration of antituberculosis drugs enables supervision to be provided more efficiently and economically with no reduction in efficacy, although daily administration provides a greater margin of safety. The evidence on effectiveness of intermittent regimens has been reviewed.[112-114] These reviews, based on several trials,[115-120] suggest that antituberculosis treatment may be given intermittently three times a week throughout the full course of therapy or twice weekly in the continuation phase without apparent loss of effectiveness. However, the WHO and The Union do not recommend the use of twice-weekly intermittent regimens because of the potentially greater consequences of missing one of the two doses.[9,11,65,121]

The evidence base for currently recommended antituberculosis drug dosages derives from human clinical trials, animal models, and pharmacokinetic and toxicity studies. The

evidence on drug dosages and safety and the biological basis for dosage recommendations have been extensively reviewed in publications by the WHO, the ATS, the CDC, and the IDSA, The Union, and others.[9-11,65 121,122] The recommended daily and thrice weekly doses are shown in Table 5.

TABLE 5.

Doses of first-line antituberculosis drugs in adults and children

Drug	Recommended dose in mg/kg body weight (range) Daily	Three times weekly
Isoniazid*		
Children	10 (10–15), maximum 300 mg/day	——
Adults	5 (4–6), maximum 300 mg/day	10 (8–12), maximum 900 mg/dose
Rifampicin		
Children	15 (10–20) maximum 600 mg/day	——
Adults	10 (8–12), maximum 600 mg/day	10 (8–12), maximum 600 mg/dose
Pyrazinamide		
Children	35 (30–40), maximum 2,000 mg/day	——
Adults	25 (20–30), maximum 2,000 mg/day	35 (30–40), maximum 3,000 mg/dose
Ethambutol		
Children	20 (15–25),* maximum 1,000 mg/day	——
Adults	15 (15–20), maximum 1,600 mg/day	30 (25–35) maximum 2,400 mg/dose

* Same dosing for treatment of active disease and preventive chemotherapy (treatment of LTBI).
** The recommended daily doses of all 4 antituberculosis medicines are higher in children than in adults, because the pharmacokinetics are different (and to achieve the same plasma concentration as in adults, the doses need to be increased)[1].

Source: *World Health Organization. Treatment of tuberculosis: guidelines*—4th ed. WHO/HTM/TB/2009. 420 World Health Organization, Geneva, 2009.

Treatment of tuberculosis in special clinical situations such the presence of liver disease, renal disease, pregnancy, and HIV infection may require modification of the standard regimen or alterations in dosage or frequency of drug administration. For guidance in these situations see the WHO and ATS/CDC/IDSA treatment guidelines.[9,10,65]

Although there is no evidence that fixed-dose combinations are superior to individual drugs, expert opinion suggests that fixed-dose combination preparations minimize inadvertent monotherapy and may decrease the frequency of acquired drug resistance and medication errors.[9,10,65] Fixed dose combinations also reduce the number of tablets to be consumed and may thereby increase patient adherence to recommended treatment regimens.[123,124]

STANDARD 9. **To assess and foster adherence, a patient-centered approach to administration of drug treatment, based on the patient's needs and mutual respect between the patient and the provider, should be developed for all patients. Supervision and support should be individualized and should draw on the full range of recommended interventions and available support services, including patient counseling and education. A central element of the patient-centered strategy is the use of measures to assess and promote adherence to the treatment regimen and to address poor adherence when it occurs. These measures should be tailored to the individual patient's circumstances and be mutually acceptable to the patient and the provider. Such measures may include direct observation of medication ingestion (directly observed treatment or DOT) and identification and training of a treatment supporter (for tuberculosis and, if appropriate, for HIV) who is acceptable and accountable to the patient and to the health system. Appropriate incentives and enablers, including financial support, may also serve to enhance treatment adherence.**

Assuming an appropriate drug regimen is prescribed, success of treatment for tuberculosis depends largely on patient adherence.

Rationale and Evidence Summary

The approach described in the standard is designed to encourage and facilitate a positive partnership between providers and patients, working together to improve adherence. Adherence to treatment is the critical factor in determining treatment success.[125] The success of treatment for tuberculosis, assuming an appropriate drug regimen is prescribed, depends largely on patient adherence to the regimen. Achieving adherence is not an easy task, either for the patient or the provider. Antituberculosis drug regimens, as described above, consist of multiple drugs given for a minimum of six months, often when the patient feels well (except, perhaps, for adverse effects of the medications). Commonly, treatments of this sort are inconsistent with the patient's cultural milieu, belief system, and living circumstances. Consequently, it is not surprising that, without appropriate treatment support, a significant proportion of patients with tuberculosis discontinue treatment before completion of the planned duration or are erratic in drug taking. Yet, failure to complete treatment for tuberculosis leads to prolonged infectivity, poor outcomes, and drug resistance.

Adherence is a multi-dimensional phenomenon determined by the interplay of several sets of factors.[125,126] In a recent systematic review of qualitative research on patient adherence to tuberculosis treatment, eight major themes were identified across the studies reviewed (Table 6).[126] These themes were then further refined into four sets of interacting factors that influence adherence, structural factors including poverty and gender discrimination, the social context, health service factors, and personal factors. From this synthesis it was concluded that a group of factors was likely to improve patient adherence. These are listed in Table 7.

TABLE 6.

Primary themes identified in a systematic review of qualitative research on adherence to tuberculosis treatment

Organization of treatment and care for TB patients

- Access to services (urban ambulatory, distance, transport)
- Health center problems (long waiting hours, queues, physical condition of clinic)
- Treatment requirements (continuity, charging for drug, number of tablets, DOT, flexibility, choice)
- Relationship between treatment provider and patient (poor follow up, increased contact, maltreatment of patients)

Interpretation of illness and wellness

- Individual interpretations of recovery
- Perceptions of TB
- Recognition of TB as a disease

Financial burden

- Conflict between work and treatment; costs of treatment; expenses exceeding available resources
- More pressing issues to attend to
- Increased expenditure on food

Knowledge, attitudes, and beliefs about treatment

- Limited understanding of treatment, duration, and consequences of default
- Beliefs about treatment efficacy
- Denial and difficulty accepting diagnosis
- Use of other medication; treatment requirements

Law and immigration

- Completion cards; impact on immigration status; fear of detention

Personal characteristics and adherence behavior

- Substance abuse
- Mental illness
- Ethnic characteristics
- Residential mobility
- Religion
- Personal motivation
- Gender
- Structured environment
- Personal agency

Side effects

- Real, anticipated, or culturally interpreted; insufficient information; insufficient communication; insufficient attention

Family, community, and household influence

- Peer influence
- Stigma
- Providing for family
- Family support
- Marriage

DOT = directly observed treatment; **TB** = tuberculosis

Source: Munro SA, Lewin S A, Smith H J, Engel M E, Fretjheim, A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med. 4: 2007; e238.

TABLE 7.

Factors likely to improve TB treatment adherence

- Increase the visibility of TB programs in the community, which may increase knowledge and improve attitudes towards TB
- Provide more information about the disease and treatment to patients and communities
- Increase support from family, peers, and social networks
- Minimize costs and unpleasantness related to clinic visits and increase flexibility and patient autonomy
- Increase flexibility in terms of patient choice of treatment plan and type of support
- Increase the patient centeredness of interactions between providers and clients
- Address ''structural'' and ''personal'' factors, for example through micro-financing and other empowerment initiatives
- Provide more information about the effects of medication to reduce the risk of patients becoming nonadherent when experiencing treatment side effects

Source: Modified from Munro SA, Lewin S A, Smith H J, Engel M E, Fretjheim, A, Volmink J. *Patient adherence to tuberculosis treatment: a systematic review of qualitative research*. PLoS Med. 4: 2007; e238.

Despite evidence to the contrary, there is a widespread tendency to focus on patient-related factors as the main cause of poor adherence.[125,126] Sociological and behavioral research during the past 40 years has shown that patients need to be supported, not blamed.[125] Less attention is paid to provider and health system-related factors. Several studies have evaluated various interventions to improve adherence to tuberculosis therapy (Table 7). There are a number of reviews that examine the evidence on the effectiveness of these interventions.[10,127-132] Among the interventions evaluated, DOT has generated the most debate and controversy.[131-133]* The third component of the global DOTS Strategy, now widely utilized worldwide, is the administration of a standardized, rifampicin-based regimen using case management interventions that are appropriate to the individual and the circumstances.[9,10,37,65,134,135] These interventions may include DOT as one of a range of measures to promote and assess adherence to treatment.

The main advantage of DOT is that treatment is carried out entirely under close, direct supervision.[129] This provides both an accurate assessment of the degree of adherence and greater assurance that the medications have actually been ingested. When a second individual directly observes a patient swallowing medications, there is greater certainty that the patient is actually receiving the prescribed medications. This approach, therefore, results in a high cure rate and a reduction in the risk of drug resistance. Also, because there is a close contact between the patient and the treatment supporter, adverse drug effects and other complications can be identified quickly and managed appropriately. Moreover, such case management can also serve to identify and assist in addressing the myriad other problems experienced by patients with tuberculosis such as under-nutrition, poor housing and loss of income, to name a few.

* There is an important distinction between directly observed treatment (DOT) and the DOTS Strategy for tuberculosis control: DOT is one of a range of measures used to promote and assess adherence to tuberculosis treatment, whereas the DOTS Strategy consists five components and forms the platform on which tuberculosis control programs are built.

The exclusive use of health facility-based DOT may be associated with disadvantages that must be taken into account in designing a patient-centered approach. For example, these disadvantages may include loss of income and time, stigma and discrimination, and physical hardship and travel difficulties, all factors that can have an important effect on adherence.[125,135] Ideally a flexible mix of health facility- and community-based DOT should be available.

In a Cochrane systematic review that synthesized the evidence from six controlled trials comparing DOT with self-administered therapy,[131,132] the authors found that patients allocated to DOT and those allocated to self-administered therapy had similar cure rates and rates of cure plus treatment completion. They concluded that direct observation of medication ingestion did not improve outcomes. In contrast, other reviews have found DOT to be associated with high cure and treatment completion rates.[127,136,137] Also, programmatic studies on the effectiveness of the DOTS Strategy have shown high rates of treatment success in several countries.[127,136-138] It is likely that these inconsistencies across reviews are due to the fact that primary studies are often unable to separate the effect of DOT alone from the overall DOTS Strategy.[125,128] In a retrospective review of programmatic results, the highest rates of success were achieved with "enhanced DOT" which consisted of "supervised swallowing" plus social supports, incentives, and enablers as part of a larger program to encourage adherence to treatment.[127] Such complex interventions are not easily evaluated within the conventional randomized controlled trial framework.[125]

Interventions other than DOT have also shown promise.[127,136-138] Interventions that used incentives, peer assistance (for example, using cured patients), repeated motivation of patients and staff training and motivation, all have been shown to improve adherence significantly.[125-127] In addition, adherence may be enhanced by provision of more comprehensive primary care (as described in the Integrated Management of Adolescent and Adult Illness [IMAAI]),[139-141] as well as by provision of specialized services such as opiate substitution for injection drug users. Providing every patient with a copy of the *PCTC* short version, in their language, may also serve to improve adherence.

Systematic reviews and extensive programmatic experience demonstrate that there is no single approach to case management that is effective for all patients, conditions, and settings. Consequently, interventions that target adherence must be tailored or customized to the particular situation and cultural context of a given patient.[125,126] Such an approach must be developed in concert with the patient to achieve optimum adherence. This patient-centered, individualized approach to treatment support is now a core element of all tuberculosis care and control efforts. It is important to note that treatment support measures, *and not the treatment regimen itself,* must be individualized to suit the unique needs of the patient.

In addition to one-on-one support for patients being treated for tuberculosis, community support is also of importance in creating a therapeutic milieu and reducing stigma.[8] Not only should the community expect that optimum treatment for tuberculosis is provided, but, also, the community should play a role in promoting conditions that facilitate and assist in ensuring that the patient will adhere to the prescribed regimen.

STANDARD 10. Response to therapy in patients with pulmonary tuberculosis should be monitored by follow-up sputum microscopy (two specimens) at the time of completion of the initial phase of treatment (two months). If the sputum smear is positive at completion of the initial phase, sputum smears should be examined again at three months and, if positive, culture and drug susceptibility testing should be performed. In patients with extrapulmonary tuberculosis and in children, the response to treatment is best assessed clinically.

Rationale and Evidence Summary

Patient monitoring and treatment supervision are two separate functions. Patient monitoring is necessary to evaluate the response of the disease to treatment and to identify adverse drug reactions. To judge response of pulmonary tuberculosis to treatment, the most expeditious method is sputum smear microscopy. Ideally, where quality-assured laboratories are available, sputum cultures, as well as smears, should be performed for monitoring.

Approximately 80% of patients with sputum smear-positive pulmonary tuberculosis should have negative sputum smears at the time of completion of the initial phase of treatment (two months of therapy).[113] Patients who remain sputum smear-positive require particular attention. A positive sputum smear at the end of the initial phase of treatment should trigger an assessment of the patient's adherence and a careful reevaluation to determine if co-morbid conditions are present that might interfere with response to treatment. However, a positive smear at the time of completion of the initial phase is not an indication to prolong this phase of treatment. If the sputum smear is positive at month two, sputum smear examination should be repeated at month three. Having a positive sputum smear after completion of three months of treatment raises the possibility of drug resistance and culture and drug susceptibility testing should be performed in a quality-assured laboratory.

Having a positive sputum smear after completion of three months of treatment raises the possibility of drug resistance and culture and drug susceptibility testing should be performed in a quality-assured laboratory.

Radiographic assessments, although used commonly, have been shown to be unreliable for evaluating response to treatment.[142] Similarly, clinical assessment can be unreliable and misleading in the monitoring of patients with pulmonary tuberculosis.[142] In patients with extrapulmonary tuberculosis and in children, clinical evaluations may be the only available means of assessing the response to treatment.

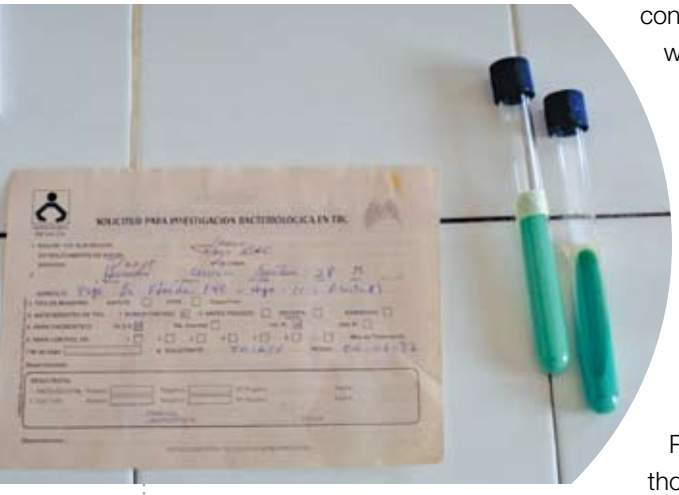
STANDARD 11. An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance, should be obtained for all patients. Drug susceptibility testing should be performed at the start of therapy for all previously treated patients. Patients who remain sputum smear-positive at completion of three months of treatment and patients who have failed, defaulted from, or relapsed following one or more courses of treatment should always be assessed for drug resistance. For patients in whom drug resistance is considered to be likely (see Table 8), culture and testing for susceptibility/resistance to at least isoniazid and rifampicin should be performed promptly. Patient counseling and education should begin immediately to minimize the potential for transmission. Infection control measures appropriate to the setting should be applied.

The strongest factor associated with drug resistance is previous antituberculosis treatment. In previously treated patients, the odds of any resistance are at least 4-fold higher, and that of MDR at least 10-fold higher, than in new (untreated) patients.

Rationale and Evidence Summary

Drug resistance is largely man-made and is a consequence of sub-optimal regimens and treatment interruptions. Clinical errors that commonly lead to the emergence of drug resistance include: failure to provide effective treatment support and assurance of adherence; failure to recognize and address patient non-adherence; inadequate drug regimens; adding a single new drug to a failing regimen; and failure to recognize existing drug resistance.[143] In addition, co-morbid conditions associated with reduced serum levels of antituberculosis drugs (e.g., malabsorption, rapid transit diarrhea, HIV infection, use of antifungal agents) may also lead to the acquisition of drug resistance.[143]

Programmatic causes of drug resistance include drug shortages and stock-outs, administration of poor-quality drugs, and lack of appropriate supervision to prevent erratic drug intake.[143] Patients with drug-resistant tuberculosis can spread the disease to their contacts. Transmission of drug-resistant strains of *M. tuberculosis* has been well described in congregate settings and in susceptible populations, notably HIV-infected persons.[144-147] However, multidrug-resistant (MDR) tuberculosis (tuberculosis caused by organisms that are resistant to at least isoniazid and rifampicin) may spread in the population at large as was shown in China, the Baltic States, and countries of the former Soviet Union.



The strongest factor associated with drug resistance is previous antituberculosis treatment, as shown by the WHO/IUATLD Global Project on Anti-TB Drug Resistance Surveillance, started in 1994.[19] In previously treated patients, the odds of any resistance are at least 4-fold higher, and that of MDR at least 10-fold higher, than in new (untreated) patients.[143] Patients with chronic tuberculosis (sputum-positive after re-treatment) and those who fail treatment (sputum-positive after five months of treatment) are at highest risk of having MDR tuberculosis, especially if rifampicin was used throughout the course of treatment.[143] Persons who are in close contact with confirmed MDR tuberculosis patients, especially children and HIV-infected individuals, also are at high risk of being infected with MDR strains. In some closed settings prisoners, persons staying in homeless shelters, and certain categories of immigrants and migrants are at increased risk of MDR tuberculosis.[143,148] These factors are summarized and presented in descending order of level of risk in Table 8.

TABLE 8.

Assessing risk for drug resistance

Risk Factors for Resistance	Comments
Failure of re-treatment regimen	Patients who are still sputum smear-positive at the end of a re-treatment regimen have perhaps the highest MDR-TB rates of any group, often exceeding 80%
Close contact with a known drug-resistant case	Most studies have shown the tuberculosis occurring in close contacts of MDR-TB patients to have high rates of MDR-TB
Failure of the initial treatment regimen	Patients who fail to become sputum smear-negative while on treatment are likely to have drug-resistant organisms. However, the likelihood depends on a number of factors, including whether rifampicin was used in the continuation phase and whether DOT was used throughout treatment. Thus, a detailed history of drugs used is essential. This is especially true for patients treated by private providers, often with non-standard regimens
Relapse after apparently successful treatment	In clinical trials most patients who relapse have fully susceptible organisms. However, under clinical program conditions, an apparent relapse, especially an early relapse, may, in fact, be an unrecognized treatment failure and thus have a higher likelihood of drug resistance
Return after default without recent treatment failure	The likelihood of MDR-TB varies substantially in this group, depending in part on the amount of treatment taken and the degree of adherence before default
Exposure in institutions that have DR-TB outbreaks or a high DR-TB prevalence	Patients who frequently stay in homeless shelters, prisoners in many countries, and health-care workers in clinics, laboratories and hospitals can have high rates of DR-TB
Residence in areas with high DR-TB prevalence	DR-TB rates in many areas of the world can be high enough to justify routine DST in all new cases

DR-TB = drug-resistant tuberculosis; **MDR-TB** = multidrug-resistant tuberculosis; **DOT** = directly observed treatment; **DST** = drug susceptibility testing

Source: Modified from World Health Organization. *Guidelines for the programmatic management of drug-resistant tuberculosis.* WHO/HTM/TB/2008.402.

By the mid-1990's, most countries participating in the global survey of antituberculosis drug resistance registered cases of MDR tuberculosis. Not surprisingly, in 2006, extensively drug-resistant (XDR) tuberculosis (defined as tuberculosis caused by *M. tuberculosis* resistant to at least isoniazid and rifampicin, as well as to any one of the fluoroquinolones and to at least one of three injectable second-line drugs [amikacin, capreomycin or kanamycin]) was described and rapidly recognized as a serious emerging threat to global public health, as well as being deadly in the initial outbreak. Subsequent reports have identified XDR tuberculosis in all regions of the world and, to date, treatment outcomes have been significantly worse than MDR tuberculosis outcomes.[149-152] In one cohort from KwaZulu-Natal, 98% of XDR tuberculosis patients co-infected with HIV died, with a median time of death of only 16 days from time of specimen collection.[149]

The two strongest risk factors for XDR tuberculosis are:

1) Failure of a tuberculosis treatment which contains second-line drugs including an injectable agent and a fluoroquinolone.
2) Close contact with an individual with documented XDR tuberculosis or with an individual for whom treatment with a regimen including second-line drugs is failing or has failed.

Drug susceptibility testing to the first-line antituberculosis drugs should be performed in laboratories that participate in an ongoing, rigorous quality assurance program. DST for first-line drugs is currently recommended for all patients with a history of previous antituberculosis treatment: patients who have failed treatment, especially those who have failed a standardized re-treatment regimen, are the highest priority.[143] Patients who develop tuberculosis and are known to have been in close contact with persons known to have MDR tuberculosis also should have DST performed on an initial isolate. Although HIV infection has not been conclusively shown to be an independent risk factor for drug resistance, MDR tuberculosis outbreaks in HIV settings and high mortality rates in persons with MDR tuberculosis and HIV infection justify routine DST in all HIV-infected tuberculosis patients, resources permitting.[143,149] All patients suspected of having XDR tuberculosis should have DST to isoniazid, rifampicin, the second-line injectable agents, and a fluoroquinolone. When epidemiological or other factors suggest that there is a risk for XDR tuberculosis in a person with HIV infection, liquid media or other validated rapid techniques for DST of first- and second-line drugs is recommended. HIV-infected patients with XDR tuberculosis have been observed to have a rapidly fatal course, thus, in such situations an empirical treatment regimen, based on international recommendations, should be initiated promptly, generally prior to having drug susceptibility test results.[149]

STANDARD 12. Patients with or highly likely to have tuberculosis caused by drug-resistant (especially MDR/XDR) organisms should be treated with specialized regimens containing second-line antituberculosis drugs. The regimen chosen may be standardized or based on suspected or confirmed drug susceptibility patterns. At least four drugs to which the organisms are known or presumed to be susceptible, including an injectable agent, should be used and treatment should be given for at least 18–24 months beyond culture conversion. Patient-centered measures, including observation of treatment, are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR/XDR tuberculosis should be obtained.

Rationale and Evidence Summary

Because randomized controlled treatment trials for MDR/XDR tuberculosis are difficult to design, none has been conducted to evaluate currently available regimens of second-line drugs. However, study designs similar to those used for new antiretroviral drugs in which a new drug plus an optimized regimen, based on DST, is compared to the optimized regimen are being used for studies of new drugs for MDR/XDR tuberculosis.[153]

In the absence of clinical trial data, current recommendations for treating MDR/XDR tuberculosis are based on observational studies, general microbiological and therapeutic principles, extrapolation from available evidence from pilot MDR tuberculosis treatment projects, and expert opinion.[143,150,154-160]

Three strategic options for treatment of MDR/XDR tuberculosis are currently recommended: standardized regimens, empiric regimens, and individualized treatment regimens. The approach is dependant on having access to either reliable DST for individual patients or population data on the prevalent resistance patterns The choice among the three approaches should be based on availability of second-line drugs and DST for first- and second-line drugs, local drug resistance patterns, and the history of use of second-line drugs.[143,160] Basic principles involved in the design of any regimen include the use of at least four drugs with either certain or highly likely effectiveness, drug administration at least six days a week, drug dosage determined by patient weight, the use of an injectable agent (an aminoglycoside or capreomycin) for at least 6 months, treatment duration of 18–24 months beyond culture conversion, and DOT throughout the treatment course.

Based on their activity, efficacy, route of administration, tolerance, availability and costs, antituberculosis drugs can be classified in five groups.[143,156] Group 1 consists of first-line drugs—isoniazid, rifampicin, ethambutol, pyrazinamide, rifabutin—if it is thought that susceptibility remains. Only one drug should be selected from Group 2 (injectable agents—kanamycin, amikacin, capreomycin, streptomycin) and Group 3 (fluoroquinolones), because of documented total or partial cross-resistance and similar toxicities within the groups. Group 4 consists of less potent oral agents—ethionamide, protionamide, cycloserine, terizidone, *p*-aminosalicylic acid. Group 5 is composed of drugs for which antituberculosis action has not been documented in clinical trials (except for thiacetazone)—clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, imipenem/cilastatin high-dose isoniazid, clarithromycin. A drug that has been used within a failing regimen should not be counted in the total of four drugs for re-treatment, even if susceptibility is shown in the laboratory.

Standardized treatment regimens are based on representative drug resistance surveillance data or on the history of drug usage in the country.[143] Based on these assessments, regimens can be designed that will have a high likelihood of success. Advantages include less dependency on highly technical laboratories, less reliance on highly specialized clinical expertise required to interpret DST results, simplified drug ordering, and easier operational implementation. A standardized approach is useful in settings where second-line drugs have not been used extensively and where resistance levels to these drugs are consequently low or absent.

Empiric treatment regimens are commonly used in specific groups of patients while the DST results are pending.[143] Unfortunately, most of the currently available DST methods have a long turnaround time. Empiric regimens are strongly recommended to avoid clinical deterioration and to prevent transmission of MDR strains of *M. tuberculosis* to contacts while awaiting the DST results.[143] Once the results of DST are known, an empiric regimen may be changed to an individualized regimen. Ongoing global efforts to address the problem of MDR tuberculosis will likely result in broader access to laboratories performing DST and a faster return of results.

Often second-line treatment is the last best hope for patients with drug-resistant tuberculosis and it is crucial that such treatment be designed for maximal effectiveness with the active participation of the patient to overcome the challenges faced by both the provider and the patient with MDR/XDR tuberculosis.

Individualized treatment regimens (based on DST profiles and drug history of individual patients or on local patterns of drug utilization) have the advantage of avoiding toxic and expensive drugs to which the MDR strain is resistant.[143] However, an individualized approach requires access to substantial human, financial, and technical (laboratory) capacity. DST for second-line drugs are notoriously difficult to perform, largely because of drug instability and the fact that critical concentrations for defining drug resistance are very close to the minimal inhibitory concentration (MIC) of individual drugs.[161] Laboratory proficiency testing results are not yet available for second-line drugs; as a result little can be said about the reliability of DST for these drugs.[143,161] Clinicians treating MDR tuberculosis patients must be aware of these limitations and interpret DST results with this in mind.

Substantial treatment support that may include financial assistance is commonly needed to enable patients to complete a second-line regimen.

Current recommendations for treatment of MDR/XDR tuberculosis can be found in World Health Organization, 2008 *Guidelines for the programmatic management of drug-resistant tuberculosis* (available at www.who.int/tb/about/en/)[143] and in Francis J. Curry National Tuberculosis Center and California Department of Public Health, *Drug-resistant Tuberculosis: A Survival Guide for Clinicians, second edition*, 2008[156] (available at www.nationaltbcenter.ucsf.edu).

MDR/XDR tuberculosis treatment is a complex health intervention and medical practitioners are strongly advised to consult colleagues experienced in the management of these patients. Often second-line treatment is the last best hope for patients with drug-resistant tuberculosis and it is crucial that such treatment be designed for maximal effectiveness with the active participation of the patient to overcome the challenges faced by both the provider and the patient with MDR/XDR tuberculosis.

STANDARD 13. A written record of all medications given, bacteriologic response, and adverse reactions should be maintained for all patients.

Rationale and Evidence Summary

There is a sound rationale for and clear benefits of a record keeping system.[162] It is common for individual physicians to believe sincerely that a majority of the patients in whom they initiate antituberculosis therapy are cured. However, when systematically evaluated, it is often seen that only a minority of patients have successfully completed the full treatment regimen.[162] The recording and reporting system enables targeted, individualized follow-up to identify patients who are failing therapy.[162] It also helps in facilitating continuity of care, particularly in settings (e.g., large hospitals) where the same practitioner might not be seeing the patient during every visit. A good record of medications given, results of investigations such as smears, cultures and chest radiographs, and progress notes on clinical improvement, adverse events and adherence will provide for more uniform monitoring and ensure a high standard of care.

Records are important to provide continuity when patients move from one care provider to another and enable tracing of patients who miss appointments. In patients who default and then return for treatment, and patients who relapse after treatment completion, it is critical to review previous records in order to assess the likelihood of drug resistance. Lastly, management of complicated cases (e.g., multidrug-resistant tuberculosis) is not possible without an adequate record of previous treatment, adverse events, and drug susceptibility results. It should be noted that, wherever patient records are concerned, care must be taken to insure confidentiality of the information, yet should be made available to the patient upon request.

In patients who default and then return for treatment, and patients who relapse after treatment completion, it is critical to review previous records in order to assess the likelihood of drug resistance.

Standards for Addressing HIV Infection and other Co-morbid Conditions

Infection with HIV both increases the likelihood of progression from infection with M. tuberculosis to active tuberculosis and changes the clinical manifestations of the disease.

STANDARD 14. HIV testing and counseling should be recommended to all patients with, or suspected of having, tuberculosis. Testing is of special importance as part of routine management of all patients in areas with a high prevalence of HIV infection in the general population, in patients with symptoms and/or signs of HIV-related conditions, and in patients having a history suggestive of high risk of HIV exposure. Because of the close relationship of tuberculosis and HIV infection, in areas of high HIV prevalence integrated approaches to prevention and treatment of both infections are recommended.

Rationale and Evidence Summary

Infection with HIV both increases the likelihood of progression from infection with *M. tuberculosis* to active tuberculosis and changes the clinical manifestations of the disease.[72,163] Further, in comparison with non-HIV-infected patients, patients with HIV infection who have pulmonary tuberculosis have a lower likelihood of having acid-fast bacilli detected by sputum smear microscopy.[72,163] Moreover, data consistently show that the chest radiographic features are atypical and the proportion of extrapulmonary tuberculosis is greater in patients with advanced HIV infection compared with those who do not have HIV infection. Consequently, knowledge of a person's HIV status influences the approach to a diagnostic evaluation for tuberculosis. For this reason it is important, particu-

larly in areas in which there is a high prevalence of HIV infection, that provider-initiated HIV testing and counseling be implemented for persons suspected of having tuberculosis and those known to have tuberculosis, as well as for patients with other conditions.[164,165] In addition, the history and physical examination should include a search for indicators that suggest the presence of HIV infection. Table 9 presents clinical features that are suggestive of HIV infection.[166] A comprehensive list of clinical criteria/algorithms for HIV/AIDS clinical staging is available in the WHO document "WHO Case Definitions Of HIV For Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children."[167]

TABLE 9.

Clinical features suggestive of HIV infection in patients with tuberculosis[165]

Past history	• Sexually transmitted infections (STI) • Herpes zoster (shingles) • Recent or recurrent pneumonia • Severe bacterial infections • Recently treated tuberculosis
Symptoms	• Weight loss (>10 kg or >20% of original weight) • Diarrhea (>1 month) • Retrosternal pain on swallowing (suggestive of esophageal candidiasis) • Burning sensation of feet (peripheral sensory neuropathy)
Signs	• Scar of herpes zoster • Itchy popular skin rash • Kaposi sarcoma • Symmetrical generalized lymphadenopathy • Oral candidiasis • Angular cheilitis • Oral hairy leukoplakia • Necrotizing gingivitis • Giant aphthous ulceration • Persistent painful genital ulceration

Source: Modified from *TB/HIV: A clinical manual.* Geneva: World Health Organization, 2004. WHO/HTM/T/2004.329.[166]

Tuberculosis is highly associated with HIV infection worldwide.[14,168] Although the prevalence of HIV infection varies widely between and within countries, among persons with HIV infection there is always an increased risk of tuberculosis. The differences in HIV prevalence mean that a variable percentage of patients with tuberculosis will have HIV infection as well. This ranges from less than 1% in low HIV prevalence countries to 50–70% in countries with a high HIV prevalence, mostly sub-Saharan African countries.[18] Even though in low HIV prevalence countries few tuberculosis patients will be HIV-infected, the connection is sufficiently strong and the impact on the patient sufficiently great that the test should always be offered in managing individual patients, especially among groups in which the prevalence of HIV is higher, such as injecting drug users. In countries having a high prevalence of HIV infection, the yield of positive results will be high and, again, the impact of a positive result on the patient will be great. Thus, the indication for HIV testing is strong; co-infected patients will benefit by access to antiretroviral therapy and by administration of cotrimoxazole for prevention of opportunistic infections.[72,163,166]

STANDARD 15. All patients with tuberculosis and HIV infection should be evaluated to determine if antiretroviral therapy is indicated during the course of treatment for tuberculosis. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. However, initiation of treatment for tuberculosis should not be delayed. Patients with tuberculosis and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.

Knowledge of a person's HIV status influences the approach to a diagnostic evaluation for tuberculosis so provider-initiated HIV testing and counseling should be implemented for persons suspected of having tuberculosis and those known to have tuberculosis.

Rationale and Evidence Summary

The evidence on effectiveness of treatment for tuberculosis in patients with HIV co-infection versus those who do not have HIV infection has been reviewed extensively.[9,10,65,110,169-172] These reviews suggest that, in general, the outcome of treatment for tuberculosis is the same in HIV-infected and non-HIV-infected patients with the notable exception that death rates are greater among patients with HIV infection, presumably due in large part to complications of HIV infection. With three exceptions tuberculosis treatment regimens are the same for HIV-infected and non-HIV-infected patients. The first exception is that thioacetazone, a drug used commonly in the past but no longer recommended, is contraindicated in patients with HIV infection. Thioacetazone is associated with a high risk of severe skin reactions in HIV-infected individuals and should not be used.[65,166] Second, the results of treatment are better if a rifampicin-containing regimen is used throughout the six-month course of treatment.[110] Third, twice-weekly continuation phase therapy should not be used for patients with advanced immunosuppression.

All patients with tuberculosis and HIV infection either currently are, or will be, candidates for antiretroviral therapy. Antiretroviral therapy results in remarkable reductions in morbidity and mortality in HIV-infected persons and may improve the outcomes of treatment for tuberculosis. Highly active antiretroviral therapy (HAART) is the internationally-accepted standard of care for persons with advanced HIV infection.[163]

In patients with HIV-related tuberculosis, treating tuberculosis is the first priority. In the setting of advanced HIV infection, untreated tuberculosis can progress rapidly to death.

All patients with tuberculosis and HIV infection either currently are, or will be, candidates for antiretroviral therapy. Antiretroviral therapy results in remarkable reductions in morbidity and mortality in HIV-infected persons.

As noted above, however, antiretroviral treatment may be lifesaving for patients with advanced HIV infection. Consequently, concurrent treatment may be necessary in patients with advanced HIV disease (e.g., circulating CD4+ T lymphocyte count <200/μL). It should be emphasized, however, that treatment for tuberculosis should not be interrupted in order to initiate antiretroviral therapy, and, in patients with early stage HIV infection, it may be safer to defer antiretroviral treatment until at least the completion of the initial phase of tuberculosis treatment.[163]

There are a number of problems associated with concomitant therapy for tuberculosis and HIV infection. These include overlapping toxicity profiles for the drugs used, drug-drug interactions (especially with rifamycins and protease inhibitors), potential problems with adherence to multiple medications, and immune reconstitution inflammatory reactions.[10,163] Consequently, consultation with an expert in HIV management is needed in deciding when to start antiretroviral drugs, the agents to use, and plan for monitoring for adverse reactions and response to both therapies. (For a single-source reference on the management of tuberculosis in patients with HIV infection see the WHO manual *TB/HIV: A Clinical Manual.*[166])

Patients with tuberculosis and HIV infection should also receive cotrimoxazole (trimethoprim-sulfamethoxazole) as prophylaxis for other infections. Several studies have demonstrated the benefits of cotrimoxazole prophylaxis, and this intervention is currently recommended by the WHO as part of the TB/HIV management package.[163,166,168,173-175]

STANDARD 16. Persons with HIV infection who, after careful evaluation, do not have active tuberculosis should be treated for presumed latent tuberculosis infection with isoniazid for six to nine months.

Rationale and Evidence Summary

Data from a recent systematic review indicate that isoniazid, given to persons with HIV infection who do not have active tuberculosis, reduces the risk of tuberculosis by approximately 33% compared with placebo.[176] The protective effect decreases with time after treatment but may persist for two to three years. The benefit is most pronounced in persons with a positive tuberculin skin test (~64% reduction) and is substantially less (14%) in persons with negative or unknown tuberculin skin test results. After excluding active tuberculosis, isoniazid (approximately 5 mg/kg/day-300 mg/day maximum) should be given to persons with HIV infection who are known to have latent tuberculosis infection or who have been in contact with an infectious tuberculosis case. If performing a tuberculin skin test is not possible, isoniazid is recommended for all persons with HIV infection who live in areas with an estimated prevalence of latent TB infection >30%.[177] More recently, evidence has shown that the combined use of isoniazid preventive therapy and antiretroviral therapy among people living with HIV significantly reduces the incidence of tuberculosis.[178]

Careful attention must be paid to excluding current active tuberculosis before starting isoniazid. Patients must be carefully questioned about symptoms that could possibly indicate the presence of active tuberculosis. These symptoms include cough, fever, night sweats, and weight loss. A physical examination should focus on chest findings and the presence or absence of focal lymphadenopathy. The usefulness of chest radiography has not been established in the screening process.[179]

STANDARD 17. All providers should conduct a thorough assessment for co-morbid conditions that could affect tuberculosis treatment response or outcome. At the time the treatment plan is developed, the provider should identify additional services that would support an optimal outcome for each patient and incorporate these services into an individualized plan of care. This plan should include assessment of and referrals for treatment of other illnesses with particular attention to those known to affect treatment outcome, for instance care for diabetes mellitus, drug and alcohol treatment programs, tobacco smoking cessation programs, and other psychosocial support services, or to such services as antenatal or well baby care.

Rationale and Evidence Summary

In addition to the location, severity and extent of tuberculosis, a number of other factors can affect the response to and outcome of treatment. These factors include concomitant illnesses (such as diabetes mellitus) psychosocial issues, and socioeconomic barriers to treatment completion.[2] In working with a patient to treat tuberculosis, the provider must assess and address other contributing factors to ensure that there is the greatest chance of cure. Addressing co-morbid conditions commonly associated with tuberculosis can decrease treatment default, prevent drug resistance, and decrease treatment failures and deaths.

There are a number of conditions that are either risk factors for tuberculosis or are common in patients with the disease. Many of these can adversely affect treatment outcome. These include HIV (discussed above), other immunosuppressive disorders, diabetes mellitus, malnutrition, alcoholism, other substance abuse, and tobacco use.[180-182] Clinicians should take individual risk factors into account and carry out the necessary tests to evaluate co-morbid conditions relevant to tuberculosis treatment response and outcome. These should be provided free of charge to the patient.

There are a number of conditions that are either risk factors for tuberculosis or are common in patients with the disease and adversely affect treatment outcome.

Social factors[125,126] may also be important in influencing treatment response and outcome, and interventions should be considered to mitigate their impact. Homelessness, social isolation, migration for work, a history of incarceration, and unemployment have all been cited as barriers to treatment adherence and risk factors for poor treatment outcome.[11,125,126] Having a diagnosis of tuberculosis may serve as an entry point to health care and psychosocial services that can enhance treatment completion. Treatment support including psychosocial support is a cornerstone of the best practices for tuberculosis treatment described in detail in *Best Practice for the Care of Patients with Tuberculosis: a guide for low-income countries.*[183] By providing patients with referrals to accessible services for co-morbid conditions of any kind, the provider enhances their chances for cure in the shortest possible time and contributes to increasing the overall health of the community.

It is recognized that not all necessary services are currently available in the areas most in need of this support. To the extent these services are available, they should be fully utilized to support tuberculosis patient treatment. Where they are not available, plans to enhance relevant capacities should be incorporated into local, regional, and national tuberculosis control strategies.

Standards for Public Health

The inability to conduct targeted contact investigations results in missed opportunities to prevent additional cases of tuberculosis, especially among children. Thus, more energetic efforts are necessary to overcome these barriers to optimum tuberculosis control practices.

STANDARD 18. All providers of care for patients with tuberculosis should ensure that persons who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. The determination of priorities for contact investigation is based on the likelihood that a contact: 1) has undiagnosed tuberculosis; 2) is at high risk of developing tuberculosis if infected; 3) is at risk of having severe tuberculosis if the disease develops; and 4) is at high risk of having been infected by the index case. The highest priority contacts for evaluation are:

- **Persons with symptoms suggestive of tuberculosis**
- **Children aged <5 years**
- **Contacts with known or suspected immunocompromised states, particularly HIV infection**
- **Contacts of patients with MDR/XDR tuberculosis**

Other close contacts are a lower priority group.

Rationale and Evidence Summary

The risk of acquiring infection with *M. tuberculosis* is correlated with intensity and duration of exposure to a person with infectious tuberculosis. Close contacts of patients with tuberculosis, therefore, are at high risk for acquiring the infection. Contact investigation is considered an important activity, both to find persons with previously undetected tuberculosis and persons who are candidates for treatment of latent tuberculosis infection.[184,185]

A systematic review of more than 50 studies on household contact investigations in high incidence settings showed that, on average, about 4.5% of the contacts were found to have active tuberculosis.[186] The median number of household contacts that were evaluated to find one case of active tuberculosis was 19 (range 14–300). The median proportion of contacts found to have latent infection was 51%[186] The median number of contacts that were evaluated to find one person with latent tuberculosis infection was 2 (range 1–14). Evidence from this review suggests that contact investigation in high incidence settings is a high-yield strategy for case finding.

Among close contacts, there are certain subgroups (e.g., children and persons with HIV infection) that are particularly at high risk for acquiring the infection with *M. tuberculosis* and progressing rapidly to active disease. Children (particularly those under the age of five years) are a vulnerable group because of the high likelihood of progressing from latent infection to active disease. Children are also more likely to develop disseminated and serious forms of tuberculosis such as meningitis. The Union, therefore, recommends that children under the age of five years living in the same household as a sputum smear-positive tuberculosis patient should be targeted for isoniazid preventive therapy (after exclusion of tuberculosis to prevent *de facto* monotherapy of tuberculosis).[102,187] Similarly, contacts who have HIV infection are at substantially greater risk for progressing to active tuberculosis. Unfortunately, lack of adequate staff and resources in many areas makes contact investigation difficult. This inability to conduct targeted contact investigations results in missed opportunities to prevent additional cases of tuberculosis, especially among children. Thus, more energetic efforts are necessary to overcome these barriers to optimum tuberculosis control practices.

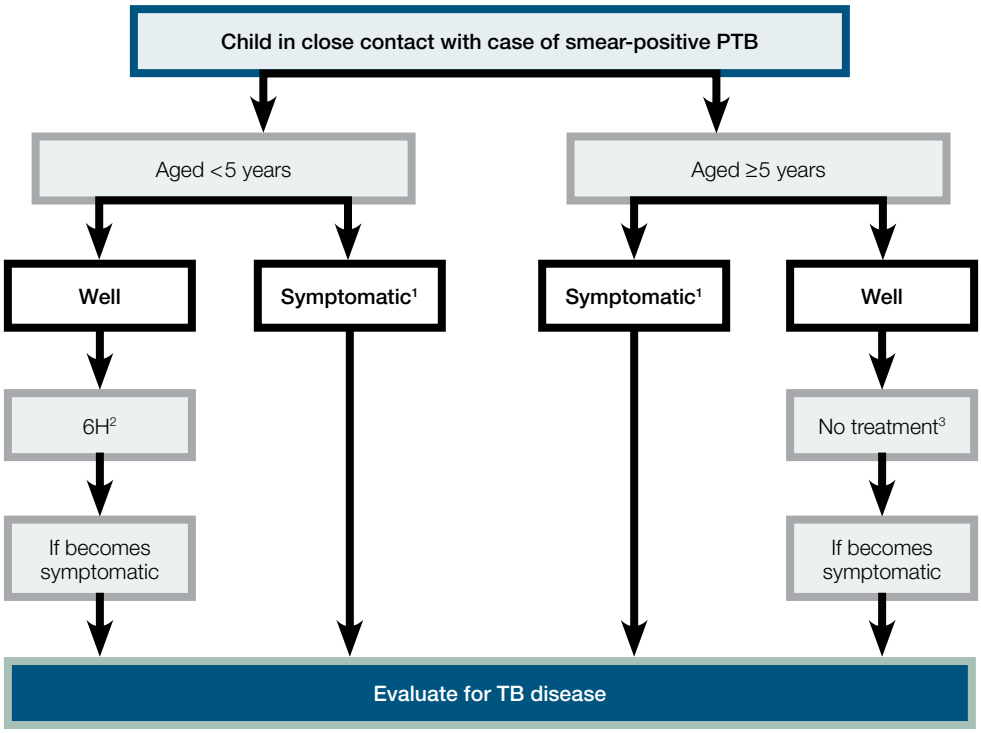
STANDARD 19. Children <5 years of age and persons of any age with HIV infection who are close contacts of an infectious index patient and who, after careful evaluation, do not have active tuberculosis, should be treated for presumed latent tuberculosis infection with isoniazid.

Rationale and Evidence Summary

Young children and persons with HIV infection are especially vulnerable to developing tuberculosis if infected and, thus, should be carefully evaluated for the presence of active tuberculosis.[187,188] To minimize the risk of their developing tuberculosis, once active disease is excluded, children <5 years of age and persons with HIV infection should be treated with isoniazid, 10 mg/kg/day (up to a maximum of 300mg) for six months on the presumption that they have been infected by the index case.[102,177] The screening of children for active tuberculosis can be accomplished by a careful medical history and physical examination, as illustrated in Figure 2. Persons with HIV infection are evaluated as described in Standard 16.

FIGURE 2.

Approach to evaluation and management of children in contact with an infectious case of tuberculosis when a tuberculin skin test (or interferon-gamma release assay) and chest radiograph are not available



1. If tuberculosis is suspected evaluate as described in Standard 6
2. Treat with isoniazid 5mg/kg/day for six months
3. No treatment should be given unless the child is HIV-infected in which case give isoniazid 5mg/kg/day

STANDARD 20. Each healthcare facility caring for patients who have, or are suspected of having, infectious tuberculosis should develop and implement an appropriate tuberculosis infection control plan.

Rationale and Evidence Summary

M. tuberculosis is spread nearly exclusively via the air, thus, the simple act of sharing air with a person who has infectious tuberculosis may result in transmission of the infection. There have been a number of well-documented outbreaks of tuberculosis including MDR and XDR tuberculosis that have occurred in healthcare facilities.[144-147] Because of the concern with transmission of both drug-resistant and drug susceptible *M. tuberculosis* in facilities providing care for patients with tuberculosis, infection control is now recognized to be of considerable importance.[189,190]

Infection control for tuberculosis consists of managerial activities at the facility level and a hierarchy of three categories of control measures including: administrative controls (most important), environmental controls, and the use of respirators (special masks designed to protect the wearer).

Managerial Controls

M. tuberculosis is spread nearly exclusively via the air, thus, the simple act of sharing air with a person who has infectious tuberculosis may result in transmission of the infection.

Facility-level managerial activities constitute the framework for setting up and implementing the other two categories of controls and should include the following: identification and strengthening of local coordinating bodies; development of a facility plan (including human resources) for implementation of infection control measures; and policies and procedures to ensure proper implementation of the control measures. In addition, policies that minimize the use of healthcare facilities, both for inpatients and outpatients, should be developed and implemented. Community approaches to providing care for persons with, or suspected of having, tuberculosis should be emphasized as a means of reducing visits to healthcare facilities.

All facilities, public and private, should have an appropriate tuberculosis infection control plan and a multidisciplinary infection control committee to guide and facilitate its implementation. Surveillance of tuberculosis cases among facility staff should be a component of the administrative controls. The plan should take into account the local epidemiology of tuberculosis, including the prevalence of HIV infection and drug resistance, if known, and should describe the specific measures to be taken and staff roles and responsibilities in implementation of the controls. Facility staff should receive basic instruction in the implementation of the infection control plan. In addition, a plan for evaluation and modification of the infection control measures should be developed. Facilities are also encouraged to participate in operational research efforts to evaluate effectiveness and rapidly respond to identified problems. Additional managerial activities include planning for appropriate construction or renovation of the building infrastructure necessary to support and facilitate infection control.

A systematic review of the literature shows that implementation of the control measures as a group reduces transmission of *M. tuberculosis* in healthcare facilities.[191] However, in healthcare facilities, administrative controls should be implemented as the first priority

Prompt collection of sputum specimens for microscopy or other microbiological evaluations is an important step in infection control. Early identification of tuberculosis leads to early initiation of treatment and a consequent reduction in infectiousness.

because they have been shown to be the most important measures in reducing transmission of tuberculosis. Consequently, all facilities, public and private, caring for patients with, or suspected of having infectious tuberculosis should implement the set of measures in a manner that is best suited to the conditions that prevail in the facility, particularly local programmatic, climatic and socioeconomic conditions. For example, infection control requirements will be less in programs that manage most patients with tuberculosis in the community compared with programs that routinely utilize hospitalization. The interventions should be consistent with and complement overall general infection control efforts and, particularly, those efforts targeting other airborne infections.

Administrative Controls

Administrative controls are a crucial category of tuberculosis infection control measures and require no structural or technological interventions to be implemented. There are several administrative controls that are feasible in all settings that, taken together, could be predicted to minimize the likelihood of transmission occurring in the facility.[190,192] Administrative measures include careful screening and early identification of patients with or suspected of having tuberculosis and separating them from other patients, especially from patients who are highly susceptible to tuberculosis. Organizing patient flow through sections of facilities, for example, rapid identification of coughing patients, placing a surgical mask on such patients, and directing them away from crowded waiting areas can minimize the potential for exposure and transmission. Separation of patients who are suspected of having tuberculosis will decrease risks to other patients and will enable health workers to take appropriate precautions. Patients living with HIV and other forms of immunosuppression, in particular, should be physically separated from those with suspected or confirmed infectious tuberculosis. Patients who have or are at risk of having MDR tuberculosis should be separated from other patients, including other patients with tuberculosis. Having a universally applied program in which patients taught proper cough etiquette will serve to reduce dissemination of infectious aerosols.

Prompt collection of sputum specimens for microscopy or other microbiological evaluations is an important step in infection control. Early identification of tuberculosis leads to early initiation of treatment and a consequent reduction in infectiousness, if the organisms causing the disease are not resistant. In areas in which there is a high prevalence of drug resistance, rapid drug susceptibility/resistance testing would enable identification and appropriate treatment for patients who otherwise would continue to be infectious because of ineffective treatment.[193] Diagnostic delays can be further minimized by using rapid tests (including rapid drug susceptibility tests), by reducing the laboratory turnaround time for sputum examination, and by carrying out diagnostic investigations (such as described in Figure 2) in parallel rather than in sequence.

All health workers should be given appropriate information and encouraged to undergo tuberculosis diagnostic investigations and HIV testing and counseling. Those who are HIV-infected should be offered appropriate prevention and care services. Health workers with HIV infection should not work in areas where exposure to untreated tuberculosis is likely and especially should not be caring for patients with known MDR and XDR tuberculosis, or in settings where drug resistance is likely. Such workers should be provided with jobs in a lower risk area.

Environmental Controls

The choice of environmental controls is largely determined by building design and intended use, construction details, local climatic and socioeconomic conditions, and available resources. Effective ventilation should be given a high priority. Ventilation effectively reduces the number of infectious particles in the air and may be achieved by natural ventilation in some settings, by mixed natural and mechanical ventilation, and by mechanical ventilation systems. The obvious benefit of natural ventilation as an approach to infection control is that can be applied to all areas that have windows and doors that open to the outside.[194] However, natural ventilation cannot be applied other than in tropical climates, and even in these areas, windows may be closed during the night negating the effect of natural ventilation, thus, it is of limited utility. In settings where optimal ventilation cannot be achieved, properly placed and shielded upper room ultraviolet germicidal irradiation fixtures should be considered as a complementary control. This may be especially useful in cold climates where outdoor ventilation is limited.

Disposable Particulate Respirators (masks)

Particulate respirators protect the person wearing the device by filtering particles out of the inspired air. Respirators that meet or exceed Centers for Disease Control and Prevention/National Institute for Occupational Services and Health (CDC/NIOSH)-certified N95 or CE-certified FFP2 standards (filter at least 95% of airborne particles ≥ 0.3 µm in diameter) should be worn by healthcare providers after appropriate training. Indications for using a respirator should be defined by the facility, but commonly include situations in which aerosols are generated, exposure to persons with untreated or ineffectively treated tuberculosis, and in situations in which administrative and environmental controls probably will not protect them from inhaling infectious airborne droplet nuclei. In areas where drug resistance is common, however, every patient with tuberculosis should be considered potentially to have drug-resistant disease for purposes of infection control.

STANDARD 21. All providers must report both new and re-treatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.

Rationale and Evidence Summary

Reporting tuberculosis cases to the local tuberculosis control program is an essential public health function, and in many countries is legally mandated. Ideally, the reporting system design, supported by a legal framework, should be capable of receiving and integrating data from several sources including laboratories and healthcare institutions, as well as from individual practitioners.

An effective reporting system enables a determination of the overall effectiveness of tuberculosis control programs, of resource needs, and of the true distribution and dynamics of the disease within the population as a whole, not just the population served by the government tuberculosis control program. In most countries tuberculosis is a reportable disease. A system of recording and reporting information on tuberculosis cases and their treatment outcomes is one of the key elements of the DOTS Strategy.[133] Such a system is useful not only to monitor progress and treatment outcomes of individual patients, but also to evaluate the overall performance of the tuberculosis control programs, at the local, national, and global levels, and to indicate programmatic weaknesses.[133]

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The recording and reporting system allows for targeted, individualized follow-up to help patients who are not making adequate progress (i.e., failing therapy).[162] The system also allows for evaluation of the performance of the practitioner, the hospital or institution, local health system, and the country as a whole. Finally, a system of recording and reporting ensures accountability.

Although, on the one hand reporting to public health authorities is essential, on the other hand it is also essential that patient confidentiality be maintained. Thus, reporting must follow predefined channels using standard procedures that guarantee that only authorized persons see the information. Such safeguards must be developed by local and national tuberculosis control programs to ensure the confidentiality of patient information.

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Annex 1

Utilization of the ISTC

Based on experience with the first edition of the *ISTC* (2006), the initial steps in utilization involve planning and formulation of specific objectives. Prior to developing activities based on the *ISTC*, the NTP must have a sound understanding of the individual standards and be willing and able to be in compliance with the standards. This likely will require internal assessment of capacity, planning, and development of specific strategies to address the standards. For example, if the goal is to involve the private sector more effectively, the NTP must be willing to adjust and accommodate, where necessary, to the needs of private providers. Planned *ISTC* activities should be clearly linked with the identified gaps to be filled. Overall objectives should also be formulated in relation to national tuberculosis control objectives and targets.

Obtaining endorsements by influential local organizations, including governments and professional societies, serves as a way of obtaining buy-in and commitment to the principles in the *ISTC*. Moreover, the influence of the *ISTC* is amplified with each endorsement received, and local endorsement paves the way for further *ISTC*-related activities, as described subsequently.

Mobilizing Professional Societies

A primary application of the *ISTC* is as a tool to unify approaches to diagnosis and treatment between the public and private sectors, especially in countries in which there is a strong private sector. Professional societies and their leaders are often influential members of the private medical community, have direct access to a large number of practicing clinicians, and have influence that extends beyond their membership. The societies often include academic physicians who are influential in their own right.

Professional societies can provide a convenient means, sometimes the only means, to access the private sector systematically by utilizing society journals, newsletters, and other communications. Strategic thinking needs to be applied in determining the reasons for seeking professional society support, but the *ISTC* can serve as a means to identify and focus on common goals and objectives and can provide a framework for addressing and improving the quality of care delivered by private providers.

Providing the Framework for Conducting a Feasibility Analysis

Because each of the major components of tuberculosis care is included in the *ISTC*, the standards provide a broad framework for a systematic "feasibility analysis" of local capabilities, and can serve as a vehicle for addressing any shortcomings. Conceptually, the *ISTC* feasibility analysis is a way for programs and providers to take stock of the standards that are or are not being met in their country. The feasibility analysis can be applied at any level in the health system national, state/provincial, district, or individual institutional level. The level at which the analysis is performed depends in part on the organization and funding of tuberculosis services. Conducting the analysis at a national level can provide an overall mapping and assessment of tuberculosis services across the country; this can be useful for general NTP planning purposes, for informing policy makers, and for advocacy efforts. Conducting the analysis at a district or local level may enable those participating

to discuss more specific problems and to devise more specific solutions. For example, if the problem is limited access to laboratories, specific sharing of resources can be suggested. Within an individual institution, the *ISTC* may be used to assess the availability and quality of essential tuberculosis services provided by the institution and by the clinicians practicing within the institution.

Quality and Performance Assessment

The individual standards within the *ISTC* can be utilized to measure the quality of tuberculosis services delivered by any provider or program. A major purpose of the *ISTC* is to improve the quality of tuberculosis care. Any or all of the standards may be used as tools for monitoring and evaluation of quality. Such assessments, just as with the feasibility analysis, can identify weaknesses in programs, institutions or individual providers. Tailored interventions can then be employed to correct the weaknesses and improve quality.

ISTC as an Advocacy Tool

Political commitment is a critical component of the DOTS Strategy, and its absence limits DOTS implementation. There has been considerable success in bringing high-level government attention and commitment to tuberculosis control. However, in most countries, at all levels of government, there has been a failure to translate this high-level political commitment into effective, country-level public policies that provide a framework for sustained tuberculosis control programs and activities. The *ISTC* provides a set of internationally recognized standards any government should seek to meet. In using the *ISTC* feasibility analysis tools, NTPs can identify gaps in meeting the standards, providing a powerful advocacy tool to seek improved tuberculosis care and control.

Engaging Patients and Communities

The *ISTC* relates to this component in two ways: First, because the *ISTC* is backed by an international consensus and it describes agreed upon elements of tuberculosis care that should be available everywhere, patients worldwide should expect that their care is in compliance with the *ISTC*. The *ISTC*, thus, provides patients with the backing they need to insist that they receive high quality care. Similarly, communities should expect that the care provided within their boundaries meets the standards, and thus is of high quality.

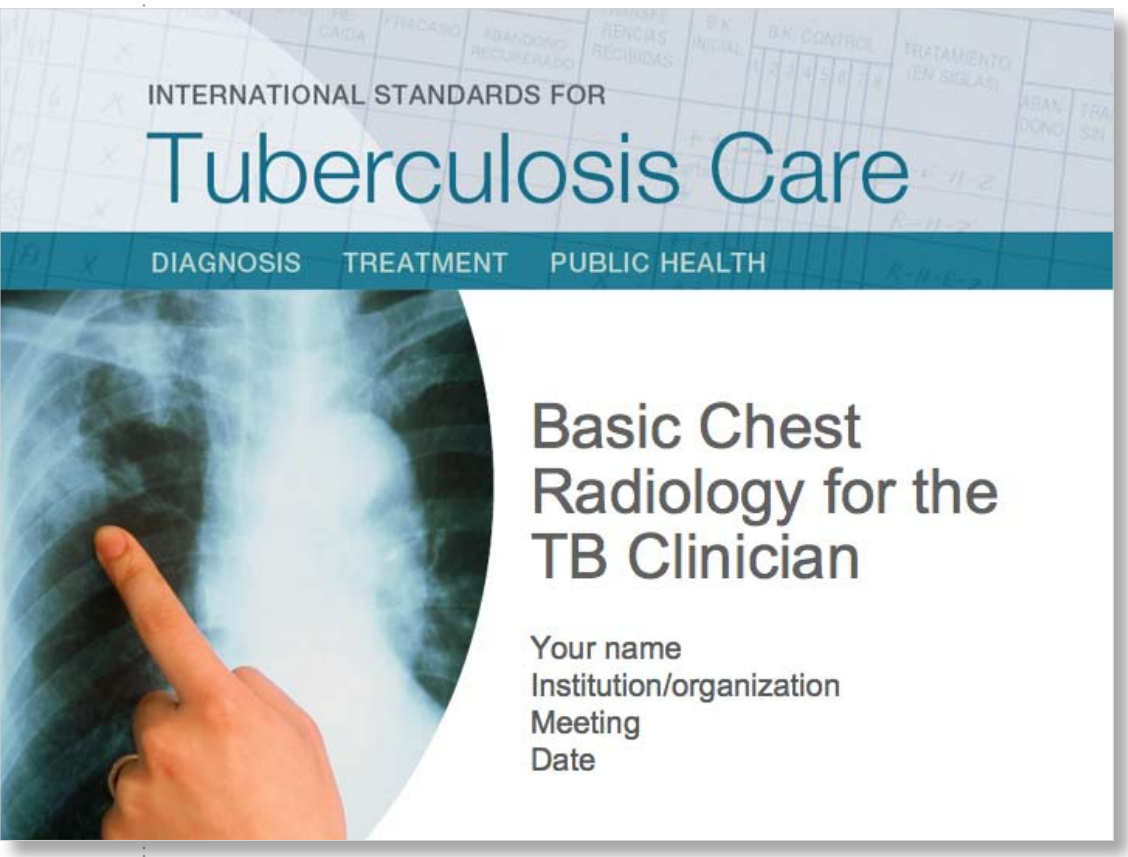
Second, the *Patients Charter for Tuberculosis Care* was developed in tandem with the *ISTC* with the intent that they would be complimentary documents. The *PCTC* relies on the *ISTC* as its technical support. The *PCTC* describes both patients' rights and responsibilities. Implicit in both the statements of patients' rights and their responsibilities is that they will receive care that is in conformance with the *ISTC*. Patients' awareness of and support for the *ISTC* and the *PCTC* can be used to provide leverage in dealings with policy makers and funding agencies, empowering them to be effective advocates for high quality tuberculosis care.

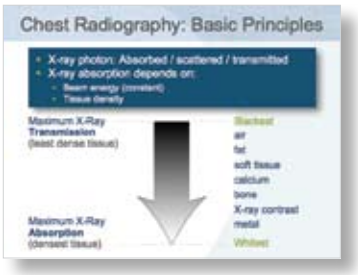
Annex 2

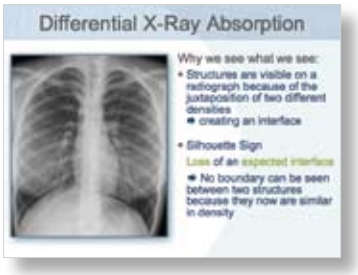
ISTC Tuberculosis Training Modules

The *ISTC Tuberculosis Training Modules* are educational resource tools developed to assist in the incorporation of the *ISTC* into training courses and curricula on tuberculosis. The material is comprehensive in its coverage of core topics in the clinical evaluation and management of tuberculosis and is presented in a format that is flexible and adaptable to various training needs. While the modules may be used as core presentations for courses on tuberculosis, the *ISTC Tuberculosis Training Modules* material should also be viewed as a tuberculosis "training resource library" offering easy access to specific *ISTC* material, individual slides, images or graphics as needed to update or augment existing tuberculosis training materials.

The planning and development of the *ISTC Tuberculosis Training Modules* was guided by members of the original *ISTC* steering committee and through significant input from *ISTC* implementation pilot countries. Through an informal assessment of needs from country-level input and steering committee members, a didactic PowerPoint slide format was chosen as most useful for easy adaptation for general training needs across a spectrum of capacity-building activities. The target audience is practicing physicians, both public and private. The modules may be adapted for pre-service trainees, nursing, and other healthcare providers.







Organization of Modules

Core topics in tuberculosis diagnosis, treatment, and public health responsibilities are covered in the modules, highlighting the relevant *ISTC* standards as they address the basic principles of care for persons with, or suspected of having, tuberculosis.

ISTC Tuberculosis Training Modules cover the following content areas:

Training Module Slide Sets 2009	
Standards for Diagnosis	
Clinical Presentation and Diagnosis of Tuberculosis	Standards 1, 2, 3, 4, 5
Microbiologic Diagnosis of Tuberculosis	Standards 2, 3, 4, 5, 6, 10, 11
Pediatric Tuberculosis	Standards 2, 3, 6
Standards for Treatment	
Initial Treatment of Tuberculosis	Standards 7, 8,10,13,17
Fostering and Assessing Adherence to Treatment	Standard 9,17
Drug-resistant Tuberculosis	Standard 11
Management of Drug-resistant Tuberculosis	Standard 12
Standards for Addressing HIV Infection and other Co-morbid Conditions	
TB and HIV infection: Introduction and Diagnosis	Standards 2, 3, 14, 19
TB and HIV infection: Treatment	Standards 8, 15,16
Standards for Public Health	
Contact Evaluation	Standards 18
Isoniazid Preventive Therapy	Standards 16, 19
Tuberculosis Infection Control	Standards 20
Additional Training Modules/Slides	
Basic Chest Radiology for the TB Clinician	
Introduction to the ISTC Standards	

Additional Training and Evaluation Tools

Additional materials provided with the slide-sets include instructor Teaching Notes, a Facilitator's Guide (includes sample *ISTC* course agendas), instructions for producing Participant Manuals, and Evaluation and Training Tools (includes Training Module Test Questions).

Teaching Notes: Each *ISTC Tuberculosis Training Module* contains Teaching Notes to assist instructors by offering speaking points, background material, and interactive tips. The Teaching Note Summary serves as a quick reference document containing a complete set of Teaching Notes with "thumbnail" slide images for all modules.

Facilitator's Guide: The *Facilitator's Guide* explains the organization of the *ISTC Tuberculosis Training Modules* and includes suggestions for effective course development and facilitation, including:

- Sample course agendas
- Participant manual instructions

Test Questions: Questions based on module objectives are included which may be used as Pre- and Post- test evaluation or alternately as interactive discussion tools for module presentations.

Other Evaluation and Training Tools: Template forms for course evaluations and training course administrative tools for registration and certification are also available.

Pilot Testing of the Training Modules

Draft versions of the *ISTC Tuberculosis Training Modules* have been pilot-tested in a variety of settings. The successful adaptation and incorporation of the *ISTC* material by these pilot groups offers examples of how the *ISTC Tuberculosis Training Modules* may be used.

Training curriculum for practicing physicians (private and public): Materials from the *ISTC Tuberculosis Training Modules* were adapted for use in a comprehensive set of training material developed to teach providers about new national tuberculosis guidelines (which incorporated the *ISTC*) in the Caribbean. In-country educators piloted the material in three separate trainings sessions.

Specialty workforce training: Select materials from the *ISTC Tuberculosis Training Modules* were used by outside experts as part of a training course for physicians, nurses, and clinical staff at a new national MDR-referral hospital in Tanzania.

Pre-service training: Collaboration between the National Tuberculosis and Leprosy Program (NTLP) and six medical schools and Allied Health Sciences in Tanzania resulted in a unified curriculum on tuberculosis integrating the *ISTC*. Materials from the *ISTC Tuberculosis Training Modules* were used in the development of the final curriculum.

Professional Societies: *ISTC Tuberculosis Training Modules* were adapted for use as core material for an extensive country-wide training plan developed by a collaborative effort of professional society members and the NTP as part of the *ISTC* taskforce mission in Indonesia.

2009 Revisions and Online Access

The first version of the training material was released in 2008. The current 2009 version has been updated to reflect the revisions within this document. New modules (radiology, pediatrics, isoniazid preventive therapy, and infection control) have been added as well. All training material can be downloaded at www.istcweb.org.

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