INTERNATIONAL STANDARDS FOR TUBERCULOSIS CARE

Draft Revised Standards (3/24/05): With References Added
World TB Day Edition

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Introduction

Although the past decade has seen substantial progress in the development and implementation of the strategies necessary for effective global tuberculosis control, tuberculosis remains an enormous and growing global health problem.[1-3] One-third of the world's population is infected with *Mycobacterium tuberculosis*, mostly in developing countries where 95% of cases occur.[2,3] In 2003, there were an estimated 8.8 million new cases of tuberculosis, of which 3.9 million were sputum smear-positive and, thus, highly infectious.[3] Alarmingly the global tuberculosis case rate is still growing, although the rate of increase is slowing.[3] Within these global data there are huge regional differences. In African countries the tuberculosis case rate continues to increase, largely because of the epidemic of HIV infection.[1,3] In many other parts of the world tuberculosis case rates are either stagnant or decreasing more slowly than should be expected because of incomplete application of effective care and control measures.

In addition to differing epidemiological circumstances, health systems differ from country to country, and care for patients with or suspected of having tuberculosis is delivered by many different types of health care providers.[4] Traditional healers in Malawi, specialist physicians in Latin America, professors of medicine in Eastern Europe, unqualified practitioners and practitioners of alternative medicine in India, national tuberculosis programs in Africa, all play roles in tuberculosis care and, therefore, in tuberculosis control. However, in spite of the differences in the ecology of tuberculosis and in the ways in which the disease is addressed, the basic principles of care for persons with or suspected of having tuberculosis are the same worldwide.

Consequently, the fundamental approaches to tuberculosis care can be described in a set of essential standards that are applicable in all areas and by all health care sectors – national tuberculosis programs, other public sector providers, and private providers.

In spite of the differences cited, tuberculosis is truly a global disease that is not confined by national boundaries; thus, effective global tuberculosis control, founded on sound principles of patient care, is a concern of all nations. Engagement of all care providers, public and private, in delivering a high standard of tuberculosis care for patients of all ages, including patients with smear-positive, smear-negative and extra-pulmonary tuberculosis, tuberculosis caused by drug resistant organisms and tuberculosis in patients with HIV infection, is essential both to protect the health of communities and to restore the health of individuals with the disease, while preventing tuberculosis in their families and others with whom they come into contact.

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. Effective treatment not only restores the health of the individual with the disease but also quickly renders the patient noninfectious and no longer a threat to the community. Thus, all providers who undertake treatment of patients with tuberculosis must recognize that they not only are treating an individual, they are assuming an important public health function that also entails a high degree of responsibility to the community.

Good care for individuals with tuberculosis is unquestionably in the best interest of the community, as well as the individual. In recognition of the community interest, community contributions to tuberculosis care and control are increasingly important in

raising public awareness of the disease, providing treatment support, reducing the stigma associated with having tuberculosis, and demanding that its health care providers adhere to a high standard of tuberculosis care.[5] The community should expect that standards of care will be provided and that, within the community, care for tuberculosis will be up to the accepted standard.

In recognition of the individual interest patients are increasingly aware of and demanding that their care be up to a high standard. A patient charter that specifies the rights and responsibilities of patients with tuberculosis is being developed as a companion to this document. This could be viewed as a standard for patients.

The intent of the standards contained in this document is to define a level of care that is consistent with successfully carrying out both the public health responsibility and providing optimal clinical care to individual patients with tuberculosis, thereby curing the patient and protecting the community. Substandard care will likely result poor patient outcomes, continued infectiousness with transmission of the infection to other community members, and, perhaps, generation and propagation of drug resistance.

The standards presented here are intended to address the essential elements of patient care and the public health responsibilities of providers. There are many situations in which the level of care can and should go beyond what is specified in these standards. Moreover, the standards do not address all clinical situations and variations in local circumstances and practices; thus, local guidelines, strategies, and resources will be necessary to facilitate meeting the standards.

Defining Standard of Care: The term “standard of care” is defined as a generally accepted level of care or set of processes that all practitioners should follow in dealing with a specific patient or disease. Care that does not reach the defined level would, therefore, be considered substandard and not acceptable. A standard differs from a guideline in that it does not provide specific guidance on disease management but, rather, presents a principle or set of principles that can be applied in all situations and that provide a platform on which care can be founded. 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 intended to assist providers in making informed decisions about appropriate health interventions.[6]

Process of Developing the Standards: Standards of care themselves must meet certain standards. A main feature of a contemporary standard is that it, where possible, must have a sound evidence base. However, in addition to being evidence-based, it must be practical and be capable of being implemented under the conditions that prevail in the areas in which it is intended to be applied. The standard must be developed by a process that is broadly inclusive of all persons with relevant perspectives. Insofar as possible decisions on content should be made by consensus. The present standard has been developed by such a process. Initially, a steering committee convened by the World Health Organization (WHO) and the American Thoracic Society (ATS) met in November 2004 to develop the scope and outline of the document. Based on the input from this group a draft was developed and presented to an expanded steering committee at a second meeting. The first draft was modified on the basis of the committee’s input and was presented to the Public-Private Mix

subgroup of the Stop TB Partnership, the Strategic and Technical Advisory Group (STAG) of the WHO Stop TB Department and to WHO's regional and country advisers. The document was modified based on the comments of each of these groups. A final draft was then presented to a joint meeting of the three implementation working groups (DOTS Expansion, Tuberculosis and HIV Infection, and MDR Tuberculosis) of the Stop TB Partnership, to the Consultants meeting of the International Union Against Tuberculosis and Lung Disease (Union) and to a special consensus conference at the time of the meeting of the Union in October 2005. As a parallel process, endorsement of the draft document (beginning after STAG review) was sought from a wide variety of organizations. The endorsing organizations to date are listed at the end of the document. *(The summaries of the meetings, list of attendees, and documents reviewed are listed on the web site of the ATS http://www.thoracic.org. A compendium of some 110 existing guidelines for tuberculosis is also listed on this site).*

Purpose, Audience, and Scope: The standards described in this document represent the essentials of tuberculosis care for persons of all ages, regardless of the setting in which the care is provided, and are directed toward all health care providers who care for persons with symptoms and signs suggestive of tuberculosis as well as for persons with tuberculosis. In addition to diagnosis and treatment, the standards address the public health responsibilities of all providers. The standards were written to accommodate local differences in practice, so long as the level of care defined in the standard is met. It is understood that to meet the standards, locally adapted approaches and strategies as determined by local circumstances and practices will be

necessary. Determining these local adaptations should be undertaken in collaboration with local and national public health authorities.

There are many sets of guidelines and recommendations that provide information on various aspects of tuberculosis care and control *(see http://www.gfmer.ch/Presentations_En/Pdf/TB%20Guidelines_Statements_Ver8_Feb2005.pdf).* This standard draws from many of these documents to provide the evidence upon which these standards are based. However, none of the existing documents presents 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.

It should be noted that in providing the evidence base for this document, not all primary data-sources are cited. Rather, in general, we have cited summaries and systematic reviews of evidence that review primary data and guidelines that have gained general acceptance by virtue of the process by which they were developed and by their broad use. Also, for the document as a whole we have used the terminology recommended in the "Revised International Definitions in Tuberculosis Control."[7] As a single-source reference for many of the practices for tuberculosis care we would refer the reader to "*Toman's Tuberculosis: Case Detection, Treatment, and Monitoring*."[8]

The Steering Committee has attempted, insofar as possible, to avoid language that would convey the perception that any of the standards is inconsistent with recommendations or guidelines developed by national or international bodies. Many of the existing documents cover a much wider range of options and present more

specific detail on approaches to diagnosis and treatment, going beyond what would be considered as essential.

The standards that follow should be seen as relating to activities that are consistent with and complementary to local and national tuberculosis control policies. However, they focus on the contribution that good clinical care of individual patients with or suspected of having tuberculosis makes to population-based tuberculosis control. In reducing the suffering and economic losses from tuberculosis, a balanced approach emphasizing both patient care and disease control is essential. This document will not address standards for national tuberculosis control programs, for personnel performance or for laboratory procedures and quality control.

Standards for Diagnosis

***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 productive cough often accompanied by ancillary symptoms such as fever, night sweats and weight loss. In addition, findings, such as lymphadenopathy, caused by concurrent extra pulmonary sites of tuberculosis may be noted, especially in patients with HIV infection.

Although most patients with pulmonary tuberculosis have cough, the symptom is not specific to tuberculosis; it can occur as part of a wide range of respiratory conditions, including acute respiratory tract infections, asthma and chronic obstructive pulmonary disease. In general acute respiratory tract infections resolve within a 2 – 3

week period, whereas, cough caused by tuberculosis and by chronic respiratory conditions persists. Although the presence of cough for 2-3 weeks is very nonspecific, traditionally, having cough of this duration has served as the criterion for defining a tuberculosis suspect and is used in most national and international guidelines, particularly in areas of moderate to high prevalence of tuberculosis. [7-10]

In a recent survey conducted in primary health care services of 9 low and middle-income countries, respiratory complaints constituted on average 18.4% of symptoms prompting a visit to a health center for persons older than 5 years. Of this group of patients 5% overall were categorized as possibly having tuberculosis because of the presence of an unexplained cough for more than 2-3 weeks.[11] Other studies have shown that 4 – 10% of adults attending out-patient health facilities in developing countries may have a persistent cough of more than 2 – 3 weeks' duration.[12] This percentage varies somewhat depending on whether there is active questioning concerning the presence of cough. Respiratory conditions, therefore, constitute a substantial proportion of the burden of diseases in patients presenting to primary health care services.[11,12]

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.[13] However, even patients with shorter duration of cough in these studies had an appreciable incidence of tuberculosis. A more recent assessment from India demonstrated that using a threshold of $\geq$ 2 weeks to prompt collection of sputum specimens the number of tuberculosis suspects increased by 61% but, more importantly, the number of cases identified increased by 46%.[14] The

results also suggested that actively inquiring as to the presence of cough in all adult clinic attendees may increase the yield of cases; 7% of patients who on questioning had cough ≥ 2 weeks had positive smears compared with 15% who without prompting volunteered that they had cough.[14]

Choosing a threshold of 2-3 weeks is an obvious trade-off, 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.[12] In countries with a low incidence of tuberculosis, it is likely that chronic cough will be due to conditions other than tuberculosis. On the other hand, in high incidence countries, tuberculosis will be one of the leading diagnoses to consider.

Overall, by focusing on persons presenting with chronic cough, the chances of identifying patients with pulmonary tuberculosis are maximized. Unfortunately, studies suggest that not all patients with respiratory symptoms receive an adequate evaluation for tuberculosis.[4] These diagnostic delays that miss opportunities for earlier detection of tuberculosis lead to increased disease severity for the patients and a greater likelihood of transmission of the infection in the community.

Standard 2. **For all patients (adults, adolescents, and children who are capable of producing sputum) suspected of having pulmonary tuberculosis, at least two and, preferably, three sputum specimens should be obtained for microscopic examination. Where resources permit and adequate laboratory facilities are available, culture should be performed in addition to microscopy.**

Rationale and Evidence Summary

The diagnosis of tuberculosis can be strongly inferred by finding acid-fast bacilli by microscopic examination of stained sputum. A microbiological diagnosis can only be confirmed by culturing *Mycobacterium tuberculosis (*or under appropriate circumstances, identifying specific nucleic acid sequences of *M. tuberculosis* in a clinical specimen). However, in nearly all clinical circumstances, finding acid-fast bacilli in stained sputum is highly specific and, thus, is the equivalent of a confirmed diagnosis. Finding acid-fast bacilli by microscopic examination or identification of *M. tuberculosis* by culture is crucial for proper patient management. Failure to perform a proper diagnostic evaluation before initiating treatment 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. It should be emphasized that, although young children cannot generally produce sputum, 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 age 15, can generally produce sputum. Thus, age alone should not be a reason for not attempting to obtain a sputum specimen from a child or adolescent.

The optimum number of sputum specimens to establish a diagnosis has been examined in a number of studies. A review shows that on average the initial specimen is positive in about 83-87% of all patients ultimately found to have acid-fast bacilli detected, in 10-12% with the second specimen, and 3-5%% on the third specimen.[15] A recent study involving 42 laboratories in four high burden countries showed that the

incremental yield from a third serial smear ranged from 0.7% to 7.2%.[16] 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 three specimens adds minimally to the number of positive specimens obtained. In addition, a third specimen is useful as confirmatory evidence if only one of the first two smears is positive.

A variety of methods have been used to improve the performance of sputum smear microscopy. Angeby and colleagues reviewed the evidence on the use of bleach to liquefy mucus followed by centrifugation to concentrate sputum.[17] They found that this method was associated with a statistically significant increase in proportion of positive tests or sensitivity of microscopy in 15 of 19 studies reviewed.[17] Another systematic review of 21 studies reporting results of various methods of concentration showed that, on average, the sensitivity of microscopy (as compared to culture) was higher with concentration by centrifugation and/or sedimentation (usually after pre-treatment with chemicals such as bleach, NAOH, and NaLC), as compared to direct smear microscopy.[18] Fifteen of 21 studies demonstrated that compared to direct smear, concentration increased the sensitivity by more than 20%. This review also evaluated data from 38 studies that reported information enabling analysis of the positivity rate (proportion of positive smears) for both the direct and concentrated smears and, thus, incremental yield. The average increase in positivity rate was 5%, with 11 of 38 studies (29%) demonstrating an increase in positivity rate of the concentrated smear of more than 15% over direct smear.[18]

Fluorescence microscopy, in which auramine-rhodamine (or phenol) staining causes the acid-fast bacilli to fluoresce against a dark background, is widely used in many parts of the world. A systematic review in which the performance of direct sputum smear microscopy using fluorescence staining was compared with Ziehl-Neelsen staining using culture as the gold standard suggests that fluorescence microscopy is the more sensitive method.[19] Both methods have a high degree of specificity. The combination of increased sensitivity with no loss of specificity makes fluorescence microscopy a more accurate test, although the increased complexity might make it less applicable.

Culture adds a significant layer of complexity and cost but also significantly increases sensitivity, resulting in increased case detection.[20] Although sputum microscopy is the first diagnostic test of choice, where resources permit and adequate laboratory facilities are available, culture should be performed in addition to microscopy. As reviewed by previously,[21,22] 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 10000 organisms per milliliter of sputum. At concentrations below 1000 organisms per milliliter of sputum, the chance of observing acid-fast bacilli in a smear is less than 10%.[21,22] In contrast, culture can detect far lower numbers of acid-fast bacilli (detection limit is about 100 organisms per ml).[20] The culture, therefore, has a much higher sensitivity than microscopy. Use of cultures, where available, will increase case detection. Further, culture makes it possible to identify the mycobacterial species and to perform drug susceptibility testing when indicated.[20]

In many countries, although culture facilities are not uniformly available, there is culture capacity in some areas. Ideally culture facilities should be available for the evaluation of at least initial specimens in all patients as well as in patients in whom drug resistance is suspected. This is a goal that national tuberculosis programs should strive for, although not yet a standard.

Traditional culture methods use egg-based solid media such as Lowenstein-Jensen. 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 color in the growth medium, 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.

Nucleic acid amplification tests (NAATs), although widely distributed, do not offer major advantages over culture at this time. While 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.[23-26] In addition, they are not sufficiently sensitive to be useful in identifying *M. tuberculosis* in specimens from extra pulmonary sites of disease.[24-26]

Other approaches to establishing a diagnosis of tuberculosis, such as serological tests, are of no proven value and should not be used in routine practice.[23]

***Standard 3*. For all patients (adults, adolescents, and children) suspected of having extra-pulmonary tuberculosis, appropriate specimens from the suspected sites of involvement, as well as sputum, should be obtained for microscopy and, where facilities and resources are available, for culture and histopathological examination.**

Rationale and Evidence Summary

Extra-pulmonary tuberculosis accounts for 15-20% of tuberculosis in populations with a low prevalence of HIV infection. The proportion of patients with HIV infection who have extra-pulmonary tuberculosis is higher. Because the clinical presentations of extra-pulmonary are often more obscure than pulmonary tuberculosis, generally, it is more of a diagnostic problem than is pulmonary tuberculosis. Nevertheless, the basic principle that bacteriological confirmation of the diagnosis should be sought still holds. Generally, there are fewer *M. tuberculosis* organisms present in extra-pulmonary sites so identification of acid-fast bacilli 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, 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 are obtained by needle biopsy of lymph nodes, are an important diagnostic tests.

***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 very nonspecific test to detect tuberculosis.[27] Radiographic examination (film or fluoroscopy) of the thorax or other suspected sites of involvement may be a useful test 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. Consequently, the use of radiographic examinations alone to "diagnose" tuberculosis is not an acceptable practice and should be discouraged.

Chest radiography is useful to evaluate persons who have negative sputum smears to attempt to identify other diseases that may be causing the symptoms. It is best used in this regard as part of a diagnostic algorithm in the diagnosis of sputum smear-negative tuberculosis. (see standard 5).

***Standard 5*. The diagnosis of sputum smear-negative pulmonary tuberculosis should be based on the following criteria: at least three negative sputum smears; chest radiography findings consistent with tuberculosis; and lack of response to a trial of broad-spectrum antimicrobial agents (excluding fluoroquinolones). In such patients, sputum cultures should be obtained. An algorithm illustrating this approach is shown in the figure below.**

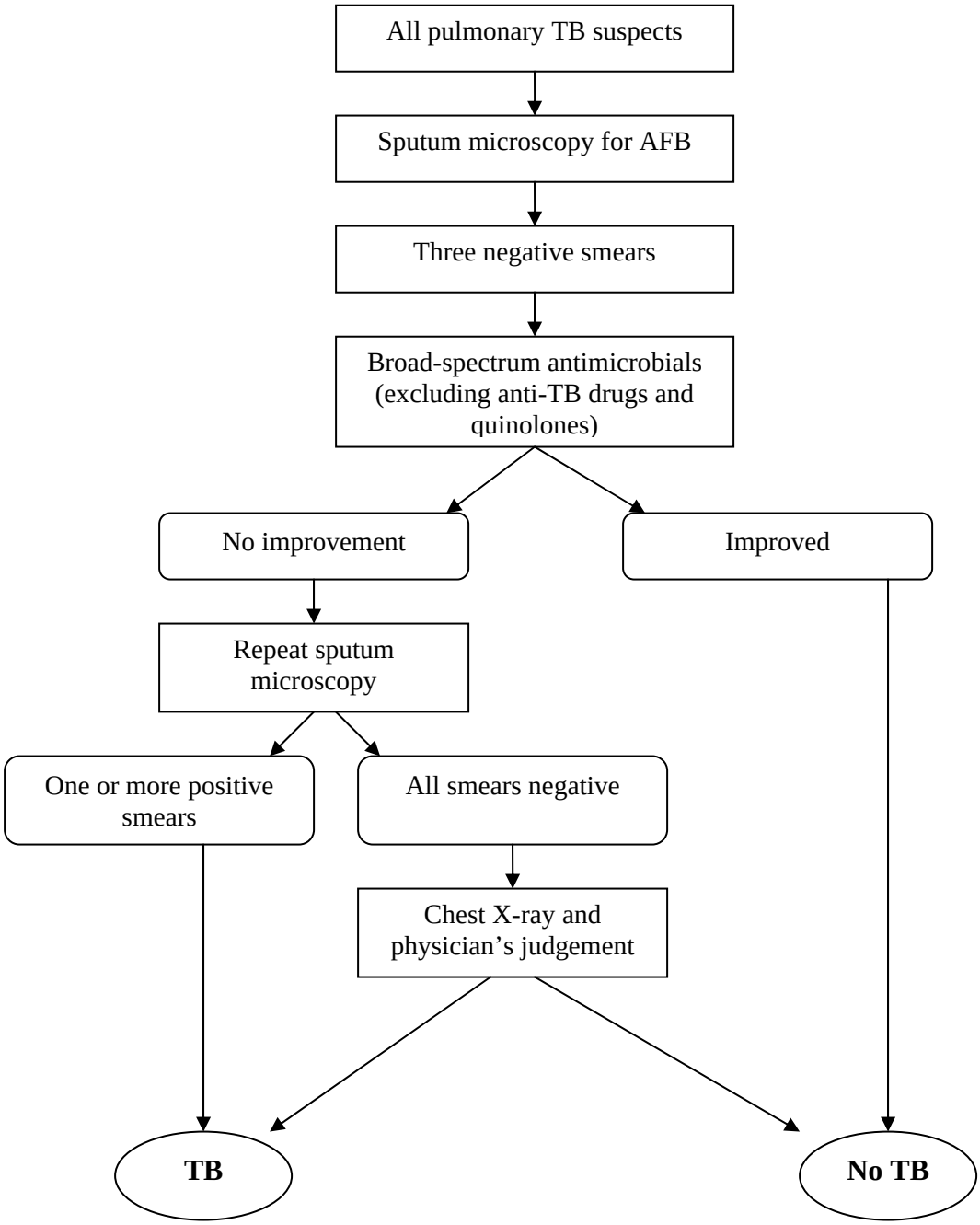
Rationale and Evidence Summary

The designation of "sputum smear-negative tuberculosis" presents a difficult diagnostic dilemma. As noted above, sputum microscopy at a given point in the patient's illness is only about 50 - 60% sensitive when compared with culture and even

less sensitive compared with a clinical diagnosis based on response to therapy. 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 three adequate sputum smears are negative. Because of the increased frequency with which patients with HIV infection and tuberculosis have negative sputum smears and because of the broad differential diagnosis of respiratory symptoms in this group, such a regimented approach is crucial.

A number of algorithms have been developed as a means of systematizing the diagnosis of smear-negative tuberculosis, although none have been adequately validated under field conditions.[28,29] The figure below is modified from an algorithm developed by WHO.[9]

Figure 1. Approach to the diagnosis of “smear-negative” tuberculosis



Source: Modified from WHO, 2003

***Standard 6*. The diagnosis of intrathoracic tuberculosis in symptomatic children with negative sputum smears is based on the finding of chest radiographic abnormalities consistent with tuberculosis, and either a history of**

exposure to an infectious case or evidence of tuberculosis infection (positive tuberculin skin test or interferon gamma release assay). Cultures of sputum or gastric lavage fluid should be obtained in such patients.

Rationale and Evidence Summary

Children with tuberculosis commonly have paucibacillary disease without significant lung cavitation but with involvement of intrathoracic lymph nodes. Consequently sputum smears are more likely to be negative and cultures of sputum or other specimens, radiographic examination of the chest and tests to detect tuberculous infection are of relatively greater importance. Because children do not cough and produce sputum effectively, cultures of gastric washings obtained by naso-gastric tube lavage has a higher yield than sputum in children, especially young children.[30]

Several recent reviews have examined the effectiveness of various diagnostic tools, scoring systems and algorithms to diagnose tuberculosis in children.[30-33] The results indicate that most of these approaches are poorly standardized, not well validated, and, thus, of limited applicability. Table 1 presents the approach recommended by the Integrated Management of Childhood Illness (IMCI) program of the WHO.[34]

Table 1. An approach to the diagnosis of tuberculosis in children

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, has HIV/AIDS, or has had measles in the past few months. Consider tuberculosis 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 (i.e. cough for more than 30 days, with or without a wheeze);
  - exposure to an adult with probable or definite pulmonary infectious tuberculosis.
- On examination:
  - fluid on one side of the chest (reduced air entry, stony 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 WHO/FCH/CAH/00.1

***Standard 7*. For all persons suspected of having tuberculosis, the clinical evaluation should include an assessment of the likelihood of HIV infection or AIDS using established criteria (such as the WHO clinical case definition criteria). Based on this assessment, as well as in areas of a generalized HIV epidemic (HIV prevalence consistently above 1% in pregnant women) and for persons known to have risk factors for HIV infection, HIV counseling and testing should be recommended.**

Rationale and Evidence Summary

Infection with HIV both increases the risk of tuberculosis and changes its clinical manifestations. A number of studies have suggested that, 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. Moreover, data consistently show that the chest radiographic features are atypical and the proportion of extra pulmonary tuberculosis is greater in patients with HIV infection

compared with those who do not have HIV infection. Consequently, knowledge of a persons HIV status would influence the approach to a diagnostic evaluation for tuberculosis. For this reason it is important, particularly in areas in which there is a high prevalence of HIV infection, for the provider to do a clinical evaluation for indicators that suggest HIV infection. Table 2 presents clinical features that are suggestive of HIV infection.[35] A comprehensive list of clinical criteria/algorithms for HIV/AIDS diagnosis is available at:

http://www.who.int/hiv/strategic/surveillance/definitions/en/

Table 2. Clinical features suggestive of HIV infection in TB patients

Past history	• Sexually transmitted infections (STI) • Herpes zoster (shingles) • Recent or recurrent pneumonia • Severe bacterial infections • Recent 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 WHO, 2004

In addition to the clinical evaluation, which should be routine for all patients, a recommendation to the patient that he/she should have HIV counseling and testing is indicated in countries in which there is a generalized HIV epidemic or for persons who acknowledge risk factors for HIV infection.

Standards for Treatment

***Standard 8*. Any care provider treating a patient for tuberculosis is assuming a public health function that includes not only prescribing an appropriate regimen but also ensuring adherence to the regimen until treatment is completed.**

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 these patients with effective treatment to ensure a rapid and lasting cure. Consequently, treatment for tuberculosis is not only a matter of individual health, such as is provided by treatment of hypertension or diabetes mellitus, for example, it is 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 an appropriate treatment regimen and the means to ensure adherence to the regimen until treatment is completed.[36] 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 9.* All patients (including those with HIV infection) who have not been treated previously should have a 2-month initial phase of treatment consisting of isoniazid, rifampicin, pyrazinamide and ethambutol. The preferred continuation phase consists of isoniazid and rifampicin given for 4 months. An alternative continuation phase regimen is isoniazid and ethambutol given for 6 months; however, this regimen is associated with a higher rate of failure and relapse, especially in patients with HIV infection.**

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.[9,10,36] These data will not be re-reviewed in this document. All of the 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 the studies that the minimum duration of treatment for smear and/or culture-positive tuberculosis is six months. For the six-month 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 of the regimens, especially in the frequency of drug administration, that have been shown to produce acceptable results.[9,10,36]

Although regimens of less than six months have been evaluated in clinical trials, a Cochrane systematic review on this topic,[37] and another review by Santha[38] found that regimens less than six months have an unacceptably high rate of relapse. The current worldwide standard, therefore, is a six-month regimen.[9,36] Although the six-month regimen is preferable, an alternative continuation phase regimen is isoniazid and ethambutol given for six months (the total duration of treatment, therefore, is eight months); however, this regimen is associated with a higher rate of failure and relapse, especially in patients with HIV infection.[39] Nevertheless the eight-month regimen may be used where limited resources do not permit supervision of rifampicin administration throughout the continuation phase.[9] A review of the outcomes of treatment of

tuberculosis in patients with HIV infection clearly shows that tuberculosis relapse is minimized by the use of a regimen containing rifampicin throughout a six-month course.[39] Thus, the eight month regimen in which rifampin is given only in the first two months should not be used in patients with HIV infection.

The evidence on effectiveness of intermittent regimens has been reviewed by Mitchison,[40] and Frieden.[41] These reviews suggest that anti-tuberculosis treatment may be given intermittently either 3 times or twice weekly without apparent loss of effectiveness. However, the WHO and IUATLD do not recommend the use of twice-weekly intermittent regimens because missing one of the two doses results in insufficient treatment.[9,10,42] A simplified version of the current WHO recommendations for treating persons who have not been treated previously is shown in Table 3.[9]

Table 3. Recommended treatment for persons not treated previously

Ranking	**Initial Phase**	**Continuation Phase**
Preferred	INH, RIF, PZA, EMB[1] daily, 2 mo.	INH, RIF daily, 4 mo INH, RIF 3x/week, 4 mo
Optional	INH, RIF, PZA, EMB daily, 2 mo	INH, EMB daily, 6 mo[2]
Optional	INH, RIF, PZA, EMB 3X/week, 2 mo	INH, RIF 3X/week, 4 mo

INH = Isoniazid, RIF = rifampicin, PZA = pyrazinamide, EMB = ethambutol

1 = streptomycin may be substituted for EMB. 2 = Associated with higher rate of treatment failure and relapse; should not be used in patients with HIV infection

***Standard 10*. The doses of anti-tuberculosis drugs used should conform to international recommendations.**

Rationale and Evidence Summary

The evidence base for currently recommended anti-tuberculosis drug dosages derives from human clinical trials, animal models, pharmacokinetic and toxicity studies. The evidence on drug dosages and safety has been extensively reviewed by the WHO,[9] the IUATLD,[10] and ATS, CDC, and IDSA.[36] The biological basis for dosage recommendation has been reviewed extensively.[9,36,40,42,43]

The recommended doses for daily and thrice weekly dosing are shown in Table 4

Table 4. Doses of First-line Antituberculosis Drugs

	Recommended dose (mg/kg)	
Drug	**Daily**	**Thrice weekly**
Isoniazid	5 (usually 300 mg)	10
Rifampicin	10 (usually 450 to 600 mg)	10 (usually 450-600 mg)
Pyrazinamide	25	35
Ethambutol	15	30
Streptomycin	15	30

***Standard 11*. A patient-centered, individualized approach to treatment support, based on the full range of recommended interventions and available support services, should be developed for all patients. A central element of the patient- centered strategy is direct observation of medication ingestion by a treatment supporter who is acceptable and accountable to the patient and to the health system.**

Rationale and Evidence summary

Adherence to treatment is a key factor in determining treatment success. In general, adherence has been defined as, “the extent to which a person’s behavior –

taking medications, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider."[44] The success of treatment for tuberculosis, assuming an appropriate drug regimen is prescribed, depends largely on patient adherence to the regimen and this is not an easy task. Antituberculosis drug regimens, as described above, consist of multiple drugs given for a minimum of six months, often when the patient feels perfectly 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 daily reality. Consequently, it is not surprising that, without appropriate treatment support, a significant proportion of patients with tuberculosis stop 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, potentially, multi-drug resistant tuberculosis.[45]

Adherence is a multi-dimensional phenomenon determined by the interplay of five sets of factors (dimensions), as illustrated in Figure 2.

Figure 2. The five dimensions of adherence

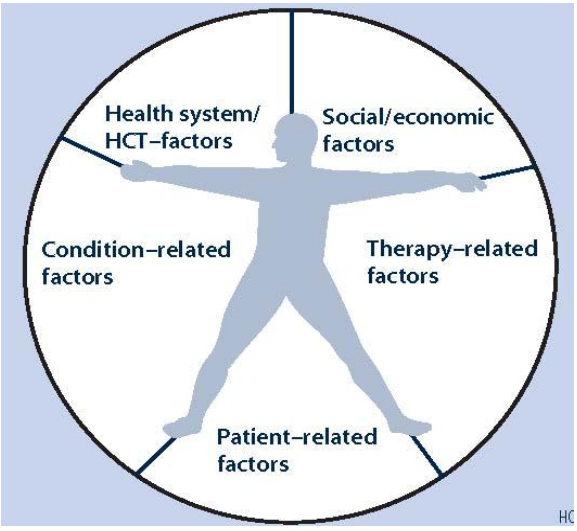


Table 4. Factors affecting adherence

Tuberculosis	**Factors affecting adherence**	**Interventions to improve adherence**
Socioeconomic-related factors	(-) Lack of effective social support networks and unstable living circumstances; culture and lay beliefs about illness and treatment; ethnicity, gender, and age; high cost of medication; high cost of transport; criminal justice involvement; involvement in drug dealing	Assessment of social needs, social support, housing, food tokens and legal measures; providing transport to treatment settings; peer assistance; mobilization of community-based organizations; optimizing the cooperation between services
Health care system/health-system-related factors	(-) Poorly developed health services; inadequate relationship between health care provider and patient; health care providers who are untrained, overworked, inadequately supervised or unsupervised in their tasks, inability to predict potentially nonadherent patients (+) Good relationships between patient and physician; availability of expertise; links with patient support systems; flexibility in the hours of operation	Uninterrupted ready availability of information; flexibility in available treatment; training and management processes that aim to improve the way providers care for patients with tuberculosis; management of disease and treatment in conjunction with the patients; multidisciplinary care; intensive staff supervision; training in adherence monitoring; DOTS strategy
Condition-related factors	(-) Asymptomatic patients; drug use; altered mental states caused by substance abuse; depression and psychological stress (+) Knowledge about TB	Education on use of medications; provision of information about tuberculosis and the need to attend for treatment
Therapy-related factors	(-) Complex treatment regimen; adverse effects of treatment; toxicity	Education on use of medications; adherence education; tailor treatment to needs of patients at risk of nonadherence; agreements (written or verbal) to return for an appointment or course of treatment; continuous monitoring and reassessment
Patient-related factors	(-) Forgetfulness; drug abuse, depression; psychological stress (+) Belief in the efficacy of treatment; motivation	Therapeutic relationship; mutual goal-setting; memory aids and reminders; incentives and/or reinforcements; reminder letters, telephone reminders or home visits for patients who default

DOT, directly observed therapy; TB, tuberculosis; (+) factors having a positive effect on adherence; (-) factors having a negative effect on adherence
Source: Modified from WHO, 2003

Despite evidence to the contrary, there is a widespread tendency to focus on patient-related factors as the main cause of poor adherence.[44] Little attention is paid to

the other provider and health system-related factors. These factors can have an important effect on adherence.[44] Sociological and behavioral research over the past 40 years has shown that patients need to be supported, not blamed.[44]

Several studies have evaluated various interventions to improve adherence to tuberculosis therapy (these interventions are listed in Table 4). The evidence on effectiveness of these interventions has been reviewed by Volmink & Garner,[46,47] WHO,[44] ATS/CDC/IDSA,[36] Chaulk and colleagues,[48] Sbarbaro,[49,50] and Gordon.[51] Among the interventions evaluated, directly observed therapy (DOT) has generated debate and controversy. As an element of patient-centered case management strategies, DOT is one of the components of DOTS, the WHO strategy for TB control. The DOTS strategy is now widely recommended as the most effective strategy for controlling tuberculosis worldwide.[7,9,36,52]

As reviewed by Sbarbaro, the main advantage of DOT is that treatment is carried out entirely under program supervision.[49] This both provides 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 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 effects and treatment complications can be identified quickly and managed appropriately.[49]

In a Cochrane systematic review, Volmink and Garner synthesized the evidence from six controlled trials that compared DOT with self-administered therapy.[46,47] The

authors found that patients allocated to DOT and those allocated to self-administered therapy had similar cure rates (RR 1.06, 95% CI 0.98, 1.14); and rates of cure plus treatment completion (RR 1.06; 95% CI 1.00, 1.13). The authors concluded that direct observation of medication ingestion did not improve outcomes.[46,47]

In contrast, other reviewers have found DOT to be associated with high cure and treatment completion rates.[9,36,48,49,53] Also, programmatic studies on the effectiveness of the DOTS strategy have shown high rates of treatment success in several countries.[44] 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.[44] As described by Chaulk and associates[48] the highest rates of success were achieved with "enhanced DOT" which consisted of "supervised swallowing" plus social supports and incentives as part of a larger program to encourage adherence to treatment. Such complex interventions are not easily evaluated within the conventional randomized controlled trial framework.[44]

As described by Gordon[51] and others,[44] interventions other than DOT have also shown promise in some research studies. For example, interventions that used incentives, peer assistance, repeated motivation of patients, and staff training and motivation all have been shown to improve adherence significantly.[51]

What is clear from these systematic reviews, plus programmatic experience, is 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 of a given patient.[44] 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 control efforts.

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.[5] Not only should the community, as noted above, expect that optimum treatment for tuberculosis is being provided, but, also, the community should expect that the patient will adhere to the prescribed regimen and recognize that they have a role in ensuring adherence.

***Standard 12*. All patients should be monitored for response to therapy, best judged in patients with pulmonary tuberculosis by follow-up sputum microscopy (two specimens) at least at the time of completion of the initial phase of treatment (two – three months), at five months, and at the end of treatment. Patients who have positive sputum smears at the time of completion of the initial phase should have monthly follow-up examinations until acid-fast organisms are no longer detected. Patients who have positive smears during the 5th month of treatment should be considered as treatment failures and have therapy modified appropriately (see standards 17 and 18).**

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. For the latter function contact between the patient and a provider is necessary. To judge response of pulmonary tuberculosis to treatment the most effective method is sputum smear microscopy. Sputum cultures, where available,

can be useful, but they are time consuming and not readily available in high burden countries.

Having a positive sputum smear at completion of at the initial phase of treatment has been shown to be predictive of a greater likelihood of treatment failure or relapse,[36] thus, repeat sputum smear examinations should be performed at monthly intervals until they become negative. Having a positive sputum smear at completion of five months of treatment defines treatment failure, indicating the need for determination of drug susceptibility and initiation of a retreatment regimen.[7] Radiographic assessment, although used commonly, have been shown to be unreliable for evaluating response to treatment.[54] Similarly, clinical assessment can be unreliable and misleading in the monitoring of patients.[54]

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

Rationale and Evidence Summary

The rationale and benefits of a record keeping system has been reviewed by Maher and Raviglione.[55] It is common for individual physicians to believe sincerely that a majority of the patients they initiate on anti-TB therapy are cured. However, when systematically evaluated, it is often seen that only a minority of patients have successfully completed the full treatment.[55] The recording and reporting system enables targeted, individualized follow-up to identify patients who are failing therapy.[55] It also helps in facilitating continuity of care, particularly in settings (e.g. large hospitals) where the same clinician might not be seeing the patient during every visit. A good record of medications given, results of investigations such as smears, culture, 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. multi-drug resistant tuberculosis) is not possible without an adequate record of previous treatment, adverse events, and drug susceptibility results.

***Standard 14*. Diagnostic HIV counseling and testing is indicated for all patients with tuberculosis as part of their routine management.**

Rationale and Evidence summary

Tuberculosis is tightly linked to HIV infection worldwide.[1] Although the prevalence of HIV infection varies very widely from country to country and within countries, among persons with HIV infection there is always an increased risk of tuberculosis. The variation in HIV prevalence means that a variable percentage of patients with tuberculosis will have HIV infection as well. This ranges from well less than 1% in low HIV prevalence countries to 50-70% in sub-Saharan African countries.[1] 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 recommended. In high HIV prevalence countries 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 testing is strong, especially now that access to

antiretroviral therapy is being greatly expanded. Because of this close connection, organizations concerned with tuberculosis and organizations concerned with HIV/AIDS recommend diagnostic HIV testing for all patients with tuberculosis.[35,56]

***Standard 15*. Patients with tuberculosis and HIV infection who are not receiving antiretroviral therapy should receive the same tuberculosis treatment regimen as those who do not have HIV infection. All patients with tuberculosis and HIV infection should be evaluated to determine if they are candidates for antiretroviral therapy. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. Given the complexity of co-administration of antituberculosis treatment and antiretroviral therapy, consultation with a physician who is expert in this area is recommended before concurrent treatment is begun.**

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.[9,35,36,39,57-59] 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. Thus, with two exceptions tuberculosis treatment regimens are the same for HIV-infected and non HIV-infected patients. The first exception is that thioacetazone 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.[9,35] Second, the results of treatment

are better if a rifampicin-containing regimen is used throughout the six-month course of treatment.[39] The eight-month course with a continuation phase of isoniazid and ethambutol should not be used in patients with HIV infection.

Many patients with tuberculosis and HIV infection will be candidates for antiretroviral therapy. Antiretroviral therapy results in dramatic 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 global standard of care.

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. 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 lymphocyte count <200/mm^3). On the other hand, in patients with early stage HIV infection, it may be safer to defer antiretroviral treatment until at least the completion of the initial intensive phase of tuberculosis treatment.[35]

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), and immune reconstitution reactions.[35,36] 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.

***Standard 16*. 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. For patients in whom drug resistance is considered to be likely, culture and drug susceptibility testing should be performed promptly.

Rationale and Evidence Summary

Evidence to be presented from DOTS Plus Guidelines under development.

***Standard 17*. Patients in whom tuberculosis is either proven to be caused by multi-drug resistant (MDR-resistant to at least isoniazid and rifampicin) organisms, or considered to be likely by clinical criteria to be MDR (chronic tuberculosis, treatment failures), should be treated with at least four drugs to which the organisms are known or presumed to be susceptible. Consultation with a provider experienced in treatment of patients with MDR tuberculosis should be obtained. Treatment should be given for at least 18 months.**

Rationale and Evidence Summary

Evidence to be presented from DOTS Plus guidelines.

Standards for Public Health Responsibilities

***Standard 18*. All providers of care for patients with tuberculosis should ensure that close contacts (especially children and persons with HIV infection) to the patient are evaluated and managed in line with international recommendations. Such contacts should be evaluated for both latent and active tuberculosis.**

Rationale and Evidence Summary

The risk of acquiring infection with *M. tuberculosis* correlates with intensity and duration of exposure to a patient with infectious tuberculosis. Close contacts of

patients with tuberculosis, therefore, at high risk for acquiring the infection. Contact investigation is considered an important public health both to find persons with previously undetected tuberculosis and persons who are candidates for treatment of latent tuberculosis infection.[60,61]

The potential yield of contact investigation in high and low incidence settings has been reviewed previously.[60,61] In low incidence settings (e.g. USA), it has been found that, on average, 5 – 10 contacts are identified for each incident tuberculosis case. Of these, about 30% are found to have latent tuberculosis infection, and another 1 – 4% will have active truberculosis.[60,62,63] As reviewed by Rieder, much higher rates of both latent infection and active disease have been reported in high incidence countries, where about 50% of household contacts have latent infection, and about 10 – 20% have active tuberculosis at the time of initial investigation.[61]

Among close contacts, there are certain subgroups that are particularly at high risk for acquiring the infection and progressing rapidly to active disease – children and persons with HIV infection. 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 (e.g. TB meningitis). The IUATLD, 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 preventive therapy (after evaluation shows no evidence of active disease).[61] Similarly, contacts with HIV infection are at substantially greater risk for progressing to active tuberculosis. Unfortunately, contact

investigation is rarely done in resource-poor, high-burden countries.[31,61] This results in missed opportunities to prevent tuberculosis among children.

***Standard 19*. All providers must report both new and retreatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with national legal requirements and policies.**

Rationale and Evidence summary

Reporting of tuberculosis cases to the tuberculosis control program is an essential public health function. This enables a determination of the overall effectiveness of tuberculosis control programs, of resource needs, and of the distribution and dynamics of the disease within the population as a whole. In most countries, tuberculosis is a reportable infectious disease. A system of recording and reporting information on tuberculosis cases and their treatment outcomes is one of the key elements of the WHO DOTS strategy.[55] 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.[55]

The rationale for a recording and reporting system has been reviewed by Maher and Raviglione.[55] It is common for individual physicians to believe sincerely that a majority of the patients they initiate on anti-TB therapy are cured. However, when systematically evaluated, it is often seen that only a minority of patients might have successfully completed the full treatment. The recording and reporting system allows for targeted, individualized follow-up to help patients who are not making adequate progress (i.e. failing therapy).[55] The system also allows for evaluation of the

performance of the clinician, the hospital or institution, local health system, and the country as a whole. Finally, the system ensures accountability.[55]

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