International Standards for Tuberculosis Care

Philip C Hopewell, Madhukar Pai, Dermot Maher, Mukund Uplekar, Mario C Raviglione

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Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, University of California, San Francisco, CA, USA (Prof P C Hopewell MD); **Francis J Curry National Tuberculosis Center, San Francisco** (P C Hopewell); **Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada** (M Pai MD); **and Stop TB Department, World Health Organization, Geneva, Switzerland** (D Maher MD, M Uplekar MD, M C Raviglione MD)

Correspondence to: Prof Philip C Hopewell, Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, San Francisco, CA 94110, USA. Tel +1 415-206-3510; fax +1 415-285-2037; **phopewell@medsfgh.ucsf.edu**

For more information on **the ISTC** see http://www.stoptb.org

Part of the reason for failing to bring about a more rapid reduction in tuberculosis incidence worldwide is the lack of effective involvement of all practitioners—public and private—in the provision of high quality tuberculosis care. While health-care providers who are part of national tuberculosis programmes have been trained and are expected to have adopted proper diagnosis, treatment, and public-health practices, the same is not likely to be true for non-programme providers. Studies of the performance of the private sector conducted in several different parts of the world suggest that poor quality care is common. The basic principles of care for people with, or suspected of having, tuberculosis are the same worldwide: a diagnosis should be established promptly; standardised treatment regimens should be used with appropriate treatment support and supervision; response to treatment should be monitored; and essential public-health responsibilities must be carried out. Prompt and accurate diagnosis, and effective treatment are essential for good patient care and tuberculosis control. All providers who undertake evaluation and treatment of patients with tuberculosis must recognise that not only are they delivering care to an individual, but they are also assuming an important public-health function. The International Standards for Tuberculosis Care (ISTC) describe a widely endorsed level of care that all practitioners should seek to achieve in managing individuals who have, or are suspected of having, tuberculosis. The document is intended to engage all care providers in delivering high quality care for patients of all ages, including those with smear-positive, smear-negative, and extra-pulmonary tuberculosis, tuberculosis caused by drug-resistant *Mycobacterium tuberculosis* complex, and tuberculosis combined with HIV infection.

Introduction

In the past decade there has been substantial progress in the development and implementation of the strategies necessary for effective tuberculosis control. However, the disease remains an enormous and growing global health problem.[1–3] Part of the reason for failing to achieve a more rapid reduction in tuberculosis incidence—even though the means to do so are well established, widely available, and embodied in the internationally recommended directly observed treatment, short course (DOTS) strategy—is the lack of involvement of practitioners outside of public-health tuberculosis control programmes in the provision of high quality tuberculosis care, in coordination with local and national control programmes.

Studies of the performance of the private sector conducted in different parts of the world suggest that poor quality care is common.[4–13] Clinicians—in particular those who work in the private health-care sector—often deviate from standard, internationally recommended, tuberculosis management practices.[11,13] These deviations include under-use of sputum smear microscopy for diagnosis (figure 1), generally associated with over-reliance on radiography; use of non-recommended drug regimens with incorrect combinations of drugs; mistakes in both drug dose and duration of treatment; and failure to supervise and assure adherence to treatment.[5–13]

Jan van den Hombergh/Lung Health Image Library

Figure 1: **Microscopic examination of a sputum sample, Ethiopia, Africa**

Full engagement of all care providers through various forms of public–private and public–public partnerships is an important component of both WHO's expanded strategy for tuberculosis control,[14] and the Global Plan to Stop TB, 2006–2015.[15] Although there have been several approaches developed for involvement of the private sector (as well as for government employed providers who are not affiliated with a tuberculosis control programme), there has been no generally agreed upon set of standards describing the essential actions that should be taken by all practitioners in providing tuberculosis services. To address this shortcoming, the International Standards for Tuberculosis Care (ISTC; panel 1)[16] were developed through a year-long inclusive process guided by a 28-member steering committee. The steering committee included individuals who represented a wide variety of relevant perspectives on tuberculosis care and control (see listing at the end of the paper). In addition, the document was presented at various public forums with an open invitation for comments. Several individuals and organisations had substantive comments, all of which were considered seriously, although not all were included in the document. It should be noted that in tandem with the development of the ISTC, a group of patient activists and advocates developed the Patients' Charter for Tuberculosis Care,[17] describing patients' rights and responsibilities. There was considerable interaction between the two groups during the course of drafting the documents.

Panel 1: **International Standards for Tuberculosis Care**[16]

Standard 1
All persons with otherwise unexplained productive cough lasting 2–3 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, and preferably three, sputum specimens obtained for microscopic examination. When possible at least one early morning specimen should be obtained.

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

Standard 4
All people 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 three negative sputum smears (including at least one early morning specimen); chest radiography 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 people with tuberculosis, they should be avoided.) For such patients, if facilities for culture are available, sputum cultures should be obtained. In people with known or suspected HIV infection the diagnostic evaluation should be expedited.

Standard 6
The diagnosis of intrathoracic (ie, pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis in symptomatic children with negative sputum smears should be 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 γ release assay). For such patients, if facilities for culture are available, sputum specimens should be obtained (by expectoration, gastric washings, or induced sputum) for culture.

Standard 7
Any practitioner treating a patient for tuberculosis is assuming an important public-health responsibility. To fulfil this responsibility the practitioner must not only prescribe an appropriate regimen, but also be capable of assessing the adherence of the patient to the regimen and addressing poor adherence when it occurs. By so doing the provider will be able to ensure adherence to the regimen until treatment is completed.

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 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol. (Ethambutol may be omitted in the initial phase of treatment for adults and children who have negative sputum smears, do not have extensive pulmonary tuberculosis or severe forms of extra-pulmonary disease, and who are known to be HIV-negative.)
The preferred continuation phase consists of isoniazid and rifampicin given for 4 months. Isoniazid and ethambutol given for 6 months is an alternative continuation phase regimen that can be used when adherence cannot be assessed but is associated with a higher rate of failure and relapse, especially in patients with HIV infection.
The doses of antituberculosis drugs used should conform to international recommendations. Fixed dose combinations of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide), and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs are highly recommended, especially when medication ingestion is not observed.

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The purpose of ISTC is to describe a widely endorsed (an up-to-date list of endorsers can be found at http://www.stoptb.org) 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 ISTC differ from existing guidelines in that they describe what should be done, whereas guidelines describe how the action is to be accomplished. The ISTC are not intended to replace either WHO or local guidelines and were written to accommodate local differences in practice. The main target audience for the ISTC is the broad group of health-care professionals who provide diagnostic and

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Standard 9
To foster and assess adherence, a patient-centred 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 gender-sensitive and age-specific and should draw on the full range of recommended interventions and available support services, including patient counselling and education. A central element of the patient-centred 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 therapy) by a treatment supporter who is acceptable and accountable to the patient and to the health system.

Standard 10
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 (2 months), at 5 months, and at the end of treatment. Patients who have positive smears during the 5th month of treatment should be considered as treatment failures and have therapy modified appropriately (see standards 14 and 15). In patients with extra-pulmonary tuberculosis and in children, the response to treatment is best assessed clinically. Follow-up radiographic examinations are usually unnecessary and might be misleading.

Standard 11
A written record of all medications given, bacteriologic response, and adverse reactions should be maintained for all patients.

Standard 12
In areas with a high prevalence of HIV infection in the general population where tuberculosis and HIV infection are likely to co-exist, HIV counselling and testing is indicated for all tuberculosis patients as part of their routine management. In areas with lower prevalence rates of HIV, HIV counselling and testing is indicated for tuberculosis patients with symptoms and/or signs of HIV-related conditions, and in tuberculosis patients having a history suggestive of high risk of HIV exposure.

Standard 13
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. 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 initiation of concurrent treatment for tuberculosis and HIV infection, regardless of which disease appeared first. However, initiation of treatment for tuberculosis should not be delayed. Patients with tuberculosis and HIV infection should also receive co-trimoxazole as prophylaxis for other infections.

Standard 14
An assessment of the likelihood of drug resistance, based on history of previous treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance, should be obtained for all patients. Patients who fail treatment and chronic cases should always be assessed for possible drug resistance. For patients in whom drug resistance is considered to be likely, culture and drug susceptibility testing for isoniazid, rifampicin, and ethambutol should be done promptly.

Standard 15
Patients with tuberculosis caused by drug-resistant (especially multidrug resistant) organisms should be treated with specialised regimens containing second-line antituberculosis drugs. At least four drugs to which the organisms are known or presumed to be susceptible should be used and treatment should be given for at least 18 months. Patient-centred measures are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR tuberculosis should be obtained.

Standard 16
All providers of care for patients with tuberculosis should ensure that people (especially children under 5 years of age and those with HIV infection) who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. Children under 5 years of age and people with HIV infection who have been in contact with an infectious case should be evaluated for both latent infection with *M tuberculosis* and for active tuberculosis.

Standard 17
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.

treatment services for tuberculosis outside of government tuberculosis programmes.

It is anticipated that the ISTC will be used as a tool to unify approaches to tuberculosis care between public (at least government tuberculosis control programmes) and private providers. Although the standards themselves should not be modified based on local circumstances, clearly there will need to be local approaches to their use and implementation. Professional medical societies are very influential in many countries, and can serve as a conduit through which the standards can be disseminated. Moreover, professional societies can serve to exert peer pressure both on their members and, when necessary, on government programmes to adhere to the ISTC. Another anticipated use of the ISTC is to serve as a focus of curricula for medical, nursing, and allied health students as well as for in-service education. There are many elements that are necessary for tuberculosis care and control to be optimally effective. These include patient and community awareness, engagement and mobilisation; access to care; availability of quality assured laboratories; appropriate information systems; and adequate primary services and health systems in general.[14] Although these elements are of substantial importance, they are beyond the scope of this set of standards, but are addressed in several other documents, particularly by the new Stop TB Strategy.[14] We anticipate that as new information emerges these standards will change. The ISTC are envisioned as a living document that will be undergoing regular review and revision.

The ISTC apply to patients of all ages, including those with smear-positive, smear-negative, and extra-pulmonary tuberculosis, tuberculosis caused by drug-resistant *Mycobacterium tuberculosis* complex organisms, and tuberculosis combined with HIV infection. A high standard of care is essential for all forms of tuberculosis to restore the health of individuals, to prevent the disease in their families and others with whom they come into contact, and to protect the health of communities.[4] The ISTC focus on the contribution that good clinical care of individual patients with, or suspected of having, tuberculosis can make to population-based tuberculosis control. A balanced approach emphasising both individual patient care and public-health principles of disease control is essential to reduce the effects on human health and economic losses caused by tuberculosis.

The basic principles of care for people with, or suspected of having, tuberculosis are the same worldwide: a diagnosis should be established promptly and accurately; standardised 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 and accurate diagnosis and effective treatment are not only essential for good patient care, they are also the key elements in the public-health response to tuberculosis. Thus, all providers who undertake evaluation and treatment of patients with tuberculosis must recognise that as well as delivering care to an individual, they are also assuming an important public-health function that entails a high level of responsibility to the community, as well as to the individual patient.

Standards for diagnosis

Standard 1

All persons with otherwise unexplained productive cough lasting 2–3 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 systemic symptoms, such as fever, night sweats, and weight loss. In a survey of primary health-care services in nine low and middle-income countries, respiratory complaints, including cough, constituted on average 18·4% of symptoms that prompted a visit to a health centre for people older than 5 years of age. Of this group, 5% of patients were categorised as possibly having tuberculosis because of the presence of an unexplained cough for more than 2–3 weeks.[18] Other studies have shown that 4–10% of adults attending outpatient health facilities in developing countries could have a persistent cough of more than 2–3 weeks' duration.[19] This percentage varies somewhat depending on whether there is active questioning concerning the presence of cough.

Data from India, Algeria, and Chile 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 more than 4 weeks.[20] 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 a using a threshold of 2 weeks or more of coughing to prompt collection of sputum specimens, the number of patients with suspected tuberculosis increased by 61%, but the number of tuberculosis cases identified increased by 46%, compared with a threshold of more than 3 weeks.[21] The results also suggested that actively inquiring as to the presence of cough in all adult clinic attendees might increase the yield of cases.[21]

Choosing a threshold of 2–3 weeks is an obvious compromise. In countries with a low prevalence of tuberculosis, it is likely that cough of this duration will be caused by 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, which are common in many areas. Unfortunately, several studies suggest that patients with subacute or chronic respiratory symptoms often receive an inadequate evaluation for tuberculosis.[5,7–10,13,22]

Standard 2

All patients (adults, adolescents, and children who are capable of producing sputum) suspected of having pulmonary tuberculosis should have at least two, and preferably three, sputum specimens obtained for microscopic examination. When possible at least one early morning specimen should be obtained.

Rationale and evidence summary

A diagnosis of tuberculosis can only be confirmed by culturing *M tuberculosis* complex (or under appropriate circumstances, identifying specific nucleic acid sequences in a clinical specimen) from any suspected site of disease. In practice, however, there are many resource-limited settings in which culture is not feasible. 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 by microscopic examination. In nearly all clinical circumstances in high prevalence areas, finding acid-fast bacilli in stained sputum is highly specific and, therefore, is the equivalent of a confirmed diagnosis.

Failure to do a proper diagnostic evaluation before initiating treatment potentially exposes the patient to the risks of unnecessary or wrong treatment with no benefit. Furthermore, such an approach could delay accurate diagnosis and proper treatment. This standard applies to adults, adolescents, and children. With proper instruction and supervision many children of 5 years of age and older can generate a specimen. Thus, age alone is not sufficient justification for failing to attempt to obtain a sputum specimen from a child or adolescent.

The optimum number of sputum specimens to establish a diagnosis has been examined in several studies. A rigorously conducted systematic review of 41 studies on this topic found that, on average, the second smear detected about 13% of smear-positive cases, and the third smear detected 4% of all smear-positive cases.[23] In studies that used culture as the reference standard, the mean incremental yield in sensitivity of the second smear was 9% and that of the third smear was 4%.[23] A recent reanalysis of data from a study involving 42 laboratories in four high burden countries showed that the incremental yield from a third sequential smear ranged from 0·7% to 7·2%.[24] The timing of specimen collection is also important. The yield appears to be greatest from early morning (overnight) specimens.[23,25–27] Therefore, at least one specimen should be obtained from an early morning collection.

A variety of methods have been used to improve the performance of sputum smear microscopy.[28] In general, the sensitivity of microscopy is higher with concentration by centrifugation, or sedimentation (usually after pre-treatment with chemicals such as bleach, sodium hydroxide, and N-acetyl-L-cysteine), or both, compared with direct smear microscopy. A systematic review of 83 studies describing the effects of various physical or chemical methods (or both) for concentrating and processing sputum before microscopy found that concentration resulted in a higher sensitivity (15–20% increase) and smear-positivity rate, when compared with direct smears.[28] Although there are advantages to concentration of sputum, there are also disadvantages. Centrifugation is more complex, requires electrical power, and could be associated with increased infection risk to laboratory personnel. Consequently, it is not clear that the advantages offset the disadvantages in low-resource settings.

A systematic review of 43 studies in which the performance of direct sputum smear microscopy with fluorescence staining was compared with Ziehl-Neelsen staining using culture as the gold standard showed that fluorescence microscopy is, on average, 10% more sensitive than conventional light microscopy and has comparable specificity.[29] The combination of increased sensitivity with little or no loss of specificity makes fluorescence microscopy a more accurate test, although the increased cost and complexity might make it less applicable in many areas. For this reason, fluorescence staining is probably best used in centres with specifically trained and proficient microscopists, where a large number of specimens are processed daily, and where there is an appropriate quality assurance programme.

Standard 3

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

Rationale and evidence summary

Because appropriate specimens might be difficult to obtain from extra-pulmonary sites, and the number of bacilli is generally low, bacteriological confirmation of extra-pulmonary tuberculosis is often more difficult than for pulmonary tuberculosis. In view of the low yield of microscopy, both culture and histopathological examination of tissue specimens, obtained by needle biopsy of lymph nodes, are important. In addition to the collection of specimens from the sites of suspected tuberculosis, sputum should be examined and a chest film obtained, especially in patients with HIV infection, in whom there is an appreciable frequency of subclinical pulmonary tuberculosis.[30]

Standard 4

All people 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 non-specific test to detect tuberculosis.[31] Radiographic examination of the

thorax or other suspected sites of involvement could be useful to identify people 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 summarised, in a study from India in which 2229 outpatients were examined by photofluorography, 227 were classified as having tuberculosis by radiographic criteria.[32,33] Of the 227, 81 (36%) had negative sputum cultures; whereas, of the remaining 2002 patients 31 (1·5%) had positive cultures. Looking at these results in terms of the sensitivity of chest radiography, 32 (20%) of 162 culture-positive cases would have been missed by radiography.

Chest radiography is useful to evaluate people who have negative sputum smears in an attempt to find evidence for pulmonary tuberculosis and to identify other abnormalities that could be responsible for the symptoms. With regards to tuberculosis, radiographic examination is most useful when applied as part of a systematic approach in the evaluation of people whose symptoms or findings, or both, suggest tuberculosis, but who have negative sputum smears.

Standard 5

The diagnosis of sputum smear-negative pulmonary tuberculosis should be based on the following criteria: at least three negative sputum smears (including at least one early morning specimen); chest radiography 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 people with tuberculosis, they should be avoided.) For such patients, if facilities for culture are available, sputum cultures should be obtained. In people with known or suspected HIV infection the diagnostic evaluation should be expedited.

Rationale and evidence summary

In view of the non-specific nature of the symptoms of tuberculosis and the multiplicity of other diseases that could be the cause of the patient's illness, a rigorous approach should be taken in diagnosing tuberculosis in a patient in whom at least three adequate sputum smears are negative. Because patients with HIV infection and tuberculosis frequently have negative sputum smears, and because of the broad differential diagnosis in this group, such a systematic approach is crucial. It is important, however, to balance the need for a systematic approach—to avoid both over-diagnosis and under-diagnosis of tuberculosis—with the need for prompt treatment in a patient with an illness that is progressing rapidly. A presumptive diagnosis of tuberculosis when the illness has another cause will delay correct diagnosis and treatment, whereas under-diagnosis will lead to more severe consequences of tuberculosis, as well as ongoing transmission of *M tuberculosis*.

A number of algorithms have been developed to diagnose smear-negative tuberculosis. Although none of the algorithms has been adequately validated under field conditions, they generally provide a useful framework for systematising the approach to diagnosis.[34,35] Of particular concern, however, is the lack of evidence on which to base approaches for the diagnosis of smear-negative tuberculosis in people with HIV infection. There are several pitfalls in using algorithms. First, strict adherence to the sequential steps of the algorithm could delay appropriate treatment in patients with an illness that is worsening rapidly. Second, studies have shown that patients with tuberculosis might respond, at least transiently, to empirical broad-spectrum antimicrobial treatment, a frequent element of diagnostic algorithms.[36–39] Obviously, such a response will lead one to delay a diagnosis of tuberculosis. Fluoroquinolones, in particular, are bactericidal for *M tuberculosis* complex. Empirical fluoroquinolone monotherapy for respiratory tract infections has been associated with delays in initiation of appropriate antituberculosis therapy and acquired resistance to the fluoroquinolones.[40] Third, the approach outlined in an algorithm might be costly to patients and deter them from continuing with the diagnostic evaluation.

Although sputum microscopy is the first bacteriological diagnostic test of choice, where resources permit, and adequate quality-assured laboratory facilities are available, culture should be included in the evaluation of patients suspected of having tuberculosis, but who have negative sputum smears. When properly done, culture increases diagnostic sensitivity, which should result in earlier case detection.[41,42] 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 widely available in most low-resource settings.

Nucleic acid amplification tests (NAATs), although widely distributed, do not offer major advantages over culture. 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.[43–49] In addition, NAATs are not of proven value in identifying *M tuberculosis* in specimens from extra-pulmonary sites of disease.[44–46,48] Other approaches for 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.[43,49]

Standard 6

The diagnosis of intrathoracic (ie, pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis in symptomatic children with negative sputum smears

should be 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 γ release assay). For such patients, if facilities for culture are available, sputum specimens should be obtained (by expectoration, gastric washings, or induced sputum) for culture.

Rationale and evidence summary

Compared with adults, sputum smears from children are more likely to be negative, and cultures of sputum or other specimens, radiographic examination of the chest, and tests to detect tuberculous infection (generally, a tuberculin skin test, or a blood-based interferon γ release assay) are of relatively greater importance. Because many children less than 5 years of age do not cough and produce sputum effectively, culture of gastric washings or induced sputum has a higher yield than spontaneous sputum.[50]

Several reviews have examined the effectiveness of various diagnostic tools, scoring systems, and algorithms to diagnose tuberculosis in children.[50–54] Many of these approaches lack standardisation and validation, and thus, are of limited applicability. Panel 2 provides a list of clinical features suggestive of tuberculosis, recommended by WHO's Integrated Management of Childhood Illness (IMCI) programme, which is widely used in first-level facilities in low and middle-income countries.[55] A systematic approach to assessing all the available diagnostic evidence is particularly important where HIV infection is common, because HIV infection compounds the diagnostic difficulties.[51,56]

***Panel 2:* Clinical features suggestive of tuberculosis in children[55]**

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. 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
- 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 reference 55.

Standards for treatment

Standard 7

Any practitioner treating a patient for tuberculosis is assuming an important public-health responsibility. To fulfil this responsibility the practitioner must not only prescribe an appropriate regimen, but also be capable of assessing the adherence of the patient to the regimen and addressing poor adherence when it occurs. By so doing the provider will be able to ensure adherence to the regimen until treatment is completed.

Rationale and evidence summary

The main interventions to prevent the spread of tuberculosis 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, it is also a matter of public health. Therefore, all providers who 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.[57] National tuberculosis programmes commonly possess approaches and tools to ensure adherence with treatment and, when properly organised, can offer these to non-programme 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 immunisations.

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 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol. (Ethambutol may be omitted in the initial phase of treatment for adults and children who have negative sputum smears, do not have extensive pulmonary tuberculosis or severe forms of extra-pulmonary disease, and who are known to be HIV-negative.)

The preferred continuation phase consists of isoniazid and rifampicin given for 4 months. Isoniazid and ethambutol given for 6 months is an alternative continuation phase regimen that can be used when adherence cannot be assessed but is associated with a higher rate of failure and relapse, especially in patients with HIV infection.

The doses of antituberculosis drugs used should conform to international recommendations. Fixed dose combinations of two (isoniazid and rifampicin), three

(isoniazid, rifampicin, and pyrazinamide), and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs are highly recommended, especially when medication ingestion is not observed.

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.[57–59] 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 or culture-positive tuberculosis, or both, is 6 months. For the 6-month treatment duration to be maximally effective, the regimen must include pyrazinamide during the initial 2-month phase and rifampicin, together with isoniazid, must be included throughout the full 6 months. There are several variations in the frequency of drug administration that have been shown to produce acceptable results.[57–59]

Two systematic reviews of regimens of less than 6 months have found that shorter durations of treatment have an unacceptably high rate of relapse.[60,61] Thus, the current international standard for smear or culture-positive tuberculosis is a regimen given for a minimum duration of 6 months.[57,59]

Although the 6-month regimen is the preferred option, an alternative continuation phase regimen, consisting of isoniazid and ethambutol given for 6 months, making the total duration of treatment 8 months, could also be used. However, it should be recognised that this regimen, presumably because of the shorter duration of rifampicin administration, is associated with a higher rate of failure and relapse, especially in patients with HIV infection.[62–64] Nevertheless, the 8-month regimen can be used when adherence to treatment throughout the continuation phase cannot be assessed.[59] The rationale for this approach is that if the patient is non-adherent, the emergence of resistance to rifampicin will be reduced. A retrospective review of the outcomes of treatment of tuberculosis in patients with HIV infection shows that tuberculosis relapse is reduced by the use of a regimen containing rifampicin throughout a 6-month course.[62] However, the patient's HIV stage, the need for, and availability of, antiretroviral drugs, and the quality of treatment supervision/support must be considered when choosing an appropriate continuation phase of therapy.

Intermittent administration of antituberculosis drugs enables supervision to be provided more efficiently and economically with no reduction in efficacy. The evidence on effectiveness of intermittent regimens has been reviewed.[65,66] These reviews, based on several trials,[67–72] suggest that antituberculosis treatment could 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 International Union Against Tuberculosis and Lung Disease (IUATLD) do not recommend the use of twice-weekly intermittent regimens because of the potentially greater consequences of missing one of the two doses.[58,59,73] A simplified version of the current WHO recommendations for treating people who have not been treated previously is shown in table 1.[59] The evidence on drug doses and safety, and the biological basis for dose recommendations, have been extensively reviewed elsewhere.[57–59,73–75] The recommended doses for daily and thrice weekly administration are shown in table 2.

Treatment of tuberculosis in special clinical situations such as the presence of liver disease, renal disease, pregnancy, and HIV infection could require modification of the standard regimen or alterations in dose or frequency of drug administration. Guidelines for these situations can be found elsewhere.[57,59]

Although there is no evidence that fixed-dose combinations are superior to individual drugs, expert opinion suggests that they reduce inadvertent monotherapy and might decrease the frequency of acquired drug resistance and medication errors.[57,59] Fixed-dose combinations also reduce the number of tablets to be consumed and could thereby increase patient adherence to recommended treatment regimens.[76,77]

Ranking	Initial phase	Continuation phase
Preferred	Isoniazid, rifampicin, pyrazinamide, ethambutol*† daily or 3 times per week for 2 months	Isoniazid, rifampicin daily or 3 times per week for 4 months
Optional	Isoniazid, rifampicin, pyrazinamide, ethambutol† daily, 2 months	Isoniazid, ethambutol daily, 6 months‡

*Streptomycin may be substituted for ethambutol. †Ethambutol may be omitted in the initial phase of treatment for adults and children who have negative sputum smears, do not have extensive pulmonary tuberculosis or severe forms of extra-pulmonary disease, and who are known to be HIV-negative. ‡Associated with higher rate of treatment failure and relapse; should generally not be used in patients with HIV infection.

Table 1: **Recommended tuberculosis treatment for people not treated previously[59]**

Drug	Recommended dose in mg/kg bodyweight (range)	
	Daily	Three times weekly
Isoniazid	5 (4–6), maximum 300 daily	10
Rifampicin	10 (8–12), maximum 600 daily	10 (8–12), maximum 600 daily
Pyrazinamide	25 (20–30)	35 (30–40)
Ethambutol	Children 20 (15–25)*, adults 15 (15–20)	30 (25–35)
Streptomycin	15 (12–18)	15 (12–18)

*The recommended daily dose of ethambutol is higher in children (20 mg/kg) than in adults (15 mg/kg), because the pharmacokinetics are different (peak serum ethambutol concentrations are lower in children than in adults receiving the same mg/kg dose).[75]

Table 2: **Doses of first-line antituberculosis drugs in adults and children**

Standard 9

To foster and assess adherence, a patient-centred 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 gender-sensitive and age-specific and should draw on the full range of recommended interventions and available support services, including patient counselling and education. A central element of the patient-centred 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 therapy [DOT]) by a treatment supporter who is acceptable and accountable to the patient and to the health system.

Gary Hampton/Lung Health Image Library

Figure 2: **A young girl supervises her mother taking her tuberculosis drugs at a clinic in New Delhi, India**

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. Assuming an appropriate drug regimen is prescribed, adherence to treatment is the crucial factor in determining treatment success.[78] This partnership between patients and providers is embodied in the Patients' Charter for Tuberculosis Care[17] developed as a companion to the ISTC. Achieving adherence is not an easy task, either for the patient or the provider. Yet, failure to complete treatment for tuberculosis leads to prolonged infectivity, poor outcomes, and drug resistance.[79]

Adherence is a multi-dimensional phenomenon determined by the interplay of five categories of factors: health system, socio-economic, therapy-related, condition-related, and patient-related.[78] Despite evidence to the contrary, there is a widespread tendency to focus on patient-related factors as the main cause of poor adherence.[78] Less attention is paid to provider and health-system-related factors. Sociological and behavioural research during the past 40 years has shown that patients need to be supported, not blamed.[78] Several studies have evaluated various interventions to improve adherence to tuberculosis therapy. There are several reviews that examine the evidence on the effectiveness of these interventions.[57,78,80–86]

Among the interventions evaluated, DOT has generated the most debate and controversy. There is an important distinction between 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 of several components and forms the platform on which tuberculosis control programmes are built.[14] A key component of the global DOTS strategy, now widely recommended as the most effective strategy for controlling tuberculosis worldwide, is the administration of a standardised, rifampicin-based regimen using case management interventions that are appropriate to the individual and the circumstances.[57,59,87] These interventions should 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 supervision.[83] 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 observes a patient swallowing medications, there is greater certainty that the patient is actually receiving the prescribed medications (figure 2). 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.[83] Moreover, such case management can also serve to identify and assist in addressing the myriad other problems experienced by patients with tuberculosis, such as undernutrition, poor housing, and loss of income.

In a Cochrane systematic review that synthesised the evidence from six controlled trials comparing DOT with self-administered therapy,[80,81] the authors found that patients allocated to DOT and those allocated to self-administered therapy had similar cure rates (relative risk [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.[80,81]

By contrast, other reviews have found DOT to be associated with high cure and treatment completion rates.[57,59,82,83,88] Also, programmatic studies on the effectiveness of the DOTS strategy have shown high rates of treatment success in several countries.[78] It is possible that these inconsistencies across reviews are because primary studies are often unable to separate the effect of

DOT alone from the overall DOTS strategy.[78,85] 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 programme to encourage adherence to treatment.[82] Such complex interventions are not easily evaluated within the conventional randomised controlled trial framework.[78]

Interventions other than DOT have also shown promise.[78,86] For example, interventions that used incentives, peer assistance, repeated motivation of patients, and staff training and motivation have all been shown to improve adherence significantly.[86] In addition, adherence might be enhanced by provision of more comprehensive primary care, as described in the Integrated Management of Adolescent and Adult Illness,[89–91] as well as by provision of specialised services such as opiate substitution for injection drug users.

Interventions that target adherence must be tailored or customised to the particular situation and cultural context of each patient.[78] Such an approach must be developed in cooperation with the patient to achieve optimum adherence. This patient-centred, individualised 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 individualised to suit the unique needs of the patient.

Standard 10

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 (2 months), at 5 months, and at the end of treatment. Patients who have positive smears during the 5th month of treatment should be considered as treatment failures and have therapy modified appropriately (see standards 14 and 15). In patients with extra-pulmonary tuberculosis and in children, the response to treatment is best assessed clinically. Follow-up radiographic examinations are usually unnecessary and might be misleading.

Rationale and evidence summary

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 done for monitoring purposes.

Having a positive sputum smear at completion of 5 months of treatment defines treatment failure, indicating the need for determination of drug susceptibility and initiation of a re-treatment regimen.[87,92,93] Radiographic assessments, although used commonly, have been shown to be unreliable for evaluating response to treatment.[94] Similarly, clinical assessment can be unreliable and misleading in the monitoring of patients with pulmonary tuberculosis.[94] In patients with extra-pulmonary tuberculosis and in children, clinical evaluations might be the only available means of assessing the response to treatment.

Standard 11

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

Rationale and evidence summary

A recording and reporting system enables targeted, individualised follow-up to identify patients who are failing therapy.[95] It also helps in facilitating continuity of care, particularly in settings 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 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 essential to review previous records to assess the likelihood of drug resistance. Lastly, management of complicated cases (eg, multidrug resistant [MDR] tuberculosis) is not possible without an adequate record of previous care. It should be noted that, wherever patient records are concerned, care must be taken to ensure confidentiality of the information.

Standard 12

In areas with a high prevalence of HIV infection in the general population where tuberculosis and HIV infection are likely to co-exist, HIV counselling and testing is indicated for all tuberculosis patients as part of their routine management. In areas with lower prevalence rates of HIV, HIV counselling and testing is indicated for tuberculosis patients with symptoms and/or signs of HIV-related conditions, and in tuberculosis patients having a history suggestive of high risk of HIV exposure.

Rationale and evidence summary

Infection with HIV changes the clinical manifestations of tuberculosis.[56,96,97] By 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.[56,96,97] Moreover, the chest radiographic features are atypical and the proportion of extra-pulmonary 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 would influence the approach to a diagnostic evaluation for tuberculosis. For this reason it is important, particularly in areas where there is a high prevalence of HIV infection, that the history and physical examination include a search for indicators that suggest the presence of HIV infection.[56,98,99]

Even though in low HIV-prevalence countries few tuberculosis patients will be HIV-infected, the connection is sufficiently strong and the effect on the patient sufficiently great that the test should always be considered in managing individual patients, especially in groups in whom the prevalence of HIV is higher, such as injecting drug users. In countries with 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 could benefit by access to antiretroviral therapy as HIV treatment programmes expand, or through administration of co-trimoxazole for prevention of opportunistic infections, even when antiretroviral drugs are not available locally.[56,100,101]

Standard 13

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. 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 initiation of concurrent treatment for tuberculosis and HIV infection, regardless of which disease appeared first. However, initiation of treatment for tuberculosis should not be delayed. Patients with tuberculosis and HIV infection should also receive co-trimoxazole as prophylaxis for other infections.

Rationale and evidence summary

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 people and may improve the outcomes of treatment for tuberculosis. Highly active antiretroviral therapy (HAART) is the internationally accepted standard of care for people with advanced HIV infection.

In patients with HIV-related tuberculosis, treating tuberculosis is the first priority. In the setting of advanced HIV infection, untreated tuberculosis can rapidly progress to death. However, antiretroviral treatment might be lifesaving for patients with advanced HIV infection. Consequently, concurrent treatment might be necessary in patients with advanced HIV disease (eg, CD4+ count <200/μL). It should be emphasised, however, that treatment for tuberculosis should not be interrupted to initiate antiretroviral therapy, and, in patients who do not have advanced HIV infection, it might be safer to defer antiretroviral treatment until at least the completion of the initial phase of tuberculosis treatment.[56]

There are a number of problems associated with concomitant therapy for tuberculosis and HIV infection. These include overlapping drug toxicity profiles, drug–drug interactions (especially with rifamycins and protease inhibitors), potential problems with adherence to multiple medications, and immune reconstitution reactions.[56,57] Consequently, consultation with an expert in HIV management is needed before deciding when to start antiretroviral drugs, the agents to use, and the plan for monitoring for adverse reactions and response to both therapies. Patients with tuberculosis and HIV infection should also receive co-trimoxazole as prophylaxis for other infections. Several studies have shown the benefits of co-trimoxazole prophylaxis, and this intervention is currently recommended by the WHO as part of the tuberculosis/HIV management package.[56,101–107]

Standard 14

An assessment of the likelihood of drug resistance, based on history of previous treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance, should be obtained for all patients. Patients who fail treatment and chronic cases should always be assessed for possible drug resistance. For patients in whom drug resistance is considered to be likely, culture and drug susceptibility testing (DST) for isoniazid, rifampicin, and ethambutol should be done promptly.

Rationale and evidence summary

Drug resistance is largely man-made and is a consequence of suboptimal 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 recognise and address patient non-adherence; inadequate drug regimens; adding a single new drug to a failing regimen; and failure to recognise existing drug resistance.[108] 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.[108]

The strongest factor associated with drug resistance is previous antituberculosis treatment.[108,109] In previously treated patients, the odds of any resistance are at least four-fold higher, and that of multiple drug resistance at least ten-fold higher, than in new (untreated) patients.[109] Patients with chronic tuberculosis (sputum positive after re-treatment) and those who fail treatment (sputum-positive after 5 months of treatment) are at highest risk of having MDR tuberculosis, especially if rifampicin was

used throughout the course of treatment.[93,109] People—especially children and HIV-infected individuals—who are in close contact with confirmed MDR tuberculosis patients are also at high risk of being infected with MDR strains. In some closed settings, prisoners, people staying in homeless shelters, and certain categories of immigrants and migrants are at increased risk of MDR tuberculosis.[108–113]

DST to the first-line antituberculosis drugs should be done in specialised reference laboratories that participate in an ongoing, rigorous quality assurance programme. 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 standardised re-treatment regimen, and chronic cases are the highest priority.[108] Patients who develop tuberculosis and are known to have been in close contact with people known to have MDR tuberculosis also should have DST done 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 people with MDR tuberculosis and HIV infection justify routine DST in all HIV-infected tuberculosis patients, resources permitting.[108]

Standard 15

Patients with tuberculosis caused by drug-resistant (especially MDR) organisms should be treated with specialised regimens containing second-line anti-tuberculosis drugs. At least four drugs to which the organisms are known or presumed to be susceptible should be used and treatment should be given for at least 18 months. Patient-centred measures are required to ensure adherence. Consultation with a provider experienced in treatment of patients with MDR tuberculosis should be obtained.

Rationale and evidence summary

Current recommendations for treatment of MDR tuberculosis are based on observational studies, general microbiological and therapeutic principles, extrapolation from available evidence from pilot MDR tuberculosis treatment projects, and expert opinion.[108,114,115] Three strategic options for treatment of MDR tuberculosis are currently recommended by WHO: standardised regimens, empirical regimens, and individualised treatment regimens.[108] The choice between these should be based on availability of second-line drugs and DST for first-line and second-line drugs, local drug resistance patterns, and the history of use of second-line drugs. Basic principles involved in the design of any regimen include use of at least four drugs with either certain or highly likely effectiveness, drug administration at least 6 days a week, drug dose determined by patient weight, the use of an injectable agent (an aminoglycoside or capreomycin sulfate) for at least 6 months, treatment duration of 18–24 months, and DOT throughout the treatment course.

Standardised treatment regimens are based on representative drug-resistance surveillance data or on the history of drug use in the country. Based on these assessments, regimens can be designed that will have a high possibility of success. Advantages include less dependency on highly technical laboratories, less reliance on highly specialised clinical expertise required to interpret DST results, simplified drug ordering, and easier operational implementation. A standardised 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.

Empirical treatment regimens are commonly used in specific groups of patients while the DST results are pending. Unfortunately, most of the available DST methods have a turnaround time of several months. Empirical 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.[108] Once the results of DST are known, an empirical regimen might be changed to an individualised regimen. Ongoing global efforts to address the problem of MDR tuberculosis will probably result in broader access to laboratories doing DST and a faster return of results.

Individualised treatment regimens (based on DST profiles and previous drug history of individual patients, or on local patterns of drug use) have the advantage of avoiding toxic and expensive drugs to which the MDR strain is resistant. However, an individualised approach requires access to substantial human, financial, and technical capacity. DST for second-line drugs are notoriously difficult to do.[116] Also, laboratory proficiency testing results are not yet available for second-line drugs, and as a result little can be said about the reliability of DST for these drugs.[109,116] Clinicians treating MDR tuberculosis patients must be aware of these limitations and interpret DST results with this in mind. MDR tuberculosis treatment is a complex health intervention and medical practitioners are strongly advised to consult colleagues experienced in the management of these patients.

Standards for public-health responsibilities

Standard 16

All providers of care for patients with tuberculosis should ensure that people (especially children under 5 years of age and those with HIV infection) who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations. Children under 5 years of age and people with HIV infection who have been in contact with an infectious case should be evaluated for both latent infection with *M tuberculosis* and for active tuberculosis.

Rationale and evidence summary

Close contacts of patients with tuberculosis are at high risk for acquiring the infection; thus, contact investigation is an important activity, both to find people with previously undetected tuberculosis and candidates for treatment of latent tuberculosis infection.[117,118] The potential yield of contact investigation in high and low incidence settings has been reviewed previously.[117,118] In low incidence settings (eg, the USA), it has been found that, on average, five to ten contacts are identified for each incident tuberculosis case. Of these, about 30% are found to have latent tuberculosis infection, and another 1–4% have active tuberculosis.[117,119,120] Much higher rates of both latent infection and active disease have been reported in high prevalence countries, where about 50% of household contacts have latent infection, and about 10–20% have active tuberculosis at the time of initial investigation.[118] A systematic review of more than 50 studies on household contact investigations in high incidence settings showed that, on average, about 6% (range 0·5% to 29%; 40 studies) of the contacts were found to have active tuberculosis.[121] The median number of household contacts that were evaluated to find one case of active tuberculosis was 19 (range 14–300).[121] The median proportion of contacts found to have latent infection was 49% (range 7% to 90%; 34 studies).[121] The median number of contacts that were evaluated to find one person with latent tuberculosis infection was two (range 1–14).[121] 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—eg, children and people 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 5 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.

Standard 17

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 programme is an essential public-health function, and in many countries is legally mandated. An effective reporting system enables an identification of the overall effectiveness of tuberculosis control programmes, 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 programme. A system of recording and reporting information on tuberculosis cases and their treatment outcomes is one of the key elements of the DOTS strategy.[95] The recording and reporting system allows for targeted, individualised follow-up to help patients who are not making adequate progress (ie, failing therapy).[95] 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. Although reporting to public-health authorities is essential, it is also essential that patient confidentiality be maintained. Thus, reporting must follow predefined channels using standard procedures that guarantee that only authorised people see the information.

Search strategy and selection criteria

Evidence summaries for each of the standards were generated by using several approaches. First, where available, existing systematic reviews (only English language) on all aspects of tuberculosis diagnosis and treatment were identified by a comprehensive search of PubMed and the Cochrane Library (both searches were up to date as of January, 2006). Second, existing evidence-based tuberculosis guidelines and recommendations were identified and compiled (a list of all the tuberculosis guidelines identified [as of February, 2005] is available at: http://www.nationaltbcenter.edu/international/). The bibliographies of these guidelines were searched as necessary. For standards where no systematic reviews or evidence-based guidelines were identified, the ISTC steering committee commissioned six systematic reviews, mostly focused on diagnostic and case finding issues (eg, smear microscopy and contact investigation). As part of these systematic reviews, the following electronic databases were searched: PubMed, Embase, Web of Science, and Biosis (searches up to date as of May, 2005). Searches of electronic databases were supplemented by hand searches of select tuberculosis journals such as the *International Journal of Tuberculosis and Lung Disease*, *Tubercle & Lung Disease*, and *Indian Journal of Tuberculosis*.

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Conflicts of interest

We declare that we have no conflicts of interest.

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The tuberculosis X factor

In this month's issue of *The Lancet Infectious Diseases* we publish the International Standards for Tuberculosis Care. When national tuberculosis control programmes and individual clinicians apply these standards correctly, multidrug-resistant tuberculosis and—the recently defined—extensively drug-resistant (XDR) tuberculosis should not develop. The term XDR tuberculosis seems first to have been used in March this year in a paper published by *Morbidity and Mortality Weekly Report* (*MMWR*). (Were the authors trying to "sex up" their report by choosing the abbreviation XDR rather than the more logical EDR?) PubMed lists only another six publications on XDR tuberculosis since March. However, huge global interest was sparked by a report at the International AIDS Conference in August of a cluster of cases in South Africa of XDR tuberculosis with high mortality among HIV co-infected patients, with a Google search finding 130 000 hits.

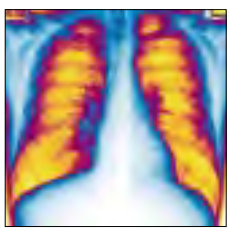
What is XDR tuberculosis, and how concerned should we be about it? As defined in *MMWR*, an XDR isolate is resistant to isoniazid and rifampicin (ie, the definition for multidrug resistance), two of the first-line antituberculosis drugs, and resistant to at least three of the six classes of second-line antimicrobials (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and para-aminosalicyclic acid). However, at a WHO meeting in Geneva on October 9–10, the definition of XDR tuberculosis was revised to resistance to isoniazid plus rifampicin, to fluoroquinolones, and to either aminoglycosides or capreomycin (a polypeptide). The *MMWR* paper reported a survey of 17 690 tuberculosis isolates collected worldwide (almost 12 000 were from South Korea) between 2000 and 2004. 3520 (19·9%) isolates were multidrug resistant, of which 347 (2%) were XDR. Among patients with XDR tuberculosis, those in the USA were 64% more likely to die during treatment than patients with the multidrug-resistant form, and those in Latvia were 54% more likely to die or have treatment failure.

Although the *MMWR* study identified XDR tuberculosis from all parts of the world, only one isolate from Africa was XDR. However, the subsequent report from the rural Msinga district of KwaZulu Natal, South Africa, described 536 patients with tuberculosis, of whom 221 had a multidrug resistant form and 53 of these were XDR. 52 of the 53 patients died, with a median survival time of just 16 days after giving a sputum sample. Genotyping studies of isolates from 46 of the 53 patients showed 39 to be genetically similar, belonging to the KwaZulu Natal family of tuberculosis strains. A cluster of cases of multidrug-resistant tuberculosis in Gauteng, South Africa, is not at present believed to involve the strain from KwaZulu Natal. However, South Africa is not alone in experiencing outbreaks of XDR tuberculosis: a recent paper in *Clinical Infectious Diseases* describes two epidemiologically related clusters of cases in Iran, and a letter in the *BMJ* reports an outbreak in Norway that has been going on for at least a decade. Concern over this emerging infectious disease prompted an expert consultation on XDR tuberculosis in South Africa on September 7–8, and the subsequent meeting in Geneva.

Although the reports of clusters of XDR tuberculosis are as yet limited, they suggest that such strains have emerged (or will emerge) in many locations and on many occasions, a worrisome development. A further concern is that with the ease of international travel, XDR strains might move rapidly from their place of origin. We need a clearer picture of the spread and frequency of emergence; indeed, one of the priorities identified by the September expert consultation was rapid country surveys of multidrug-resistant and XDR tuberculosis with the next 3–6 months.

Ever since it has been possible to treat tuberculosis with antimicrobials, it has been clear that drug resistance emerges as a result of poor prescribing practices and suboptimal control programmes. Organisms exposed to just one antibacterial drug—or substandard doses of several drugs—will acquire resistance by genetic mutation, and further suboptimal exposure to additional agents will encourage accumulation of multiple levels of resistance. The International Standards for Tuberculosis Care are designed to ensure that patients receive proper diagnosis, therapy, and support to complete their treatment regimens. The emergence of XDR tuberculosis shows that proper standards of tuberculosis care are far from being universally applied, and is a timely reminder that governments must provide the support necessary to treat properly what is essentially a curable disease.

■ *The Lancet Infectious Diseases*



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For the **MMWR paper**, see *MMWR Morb Mortal Wkly Rep* 2006; **55:** 301–05; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5511a2.htm

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For **Clinical Infectious Diseases paper**, see *Clin Infect Dis* 2006; **43:** 841–47; DOI: 10.1086/507542

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