Tuberculosis

Practical guide for clinicians, nurses,
laboratory technicians and medical auxiliaries

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Tuberculosis

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Foreword

Tuberculosis is a disease that caregivers in poor countries face every day. Its treatment does not necessarily require a vertical programme, and should be a part of regular medical activities, even when the number of patients is limited.

Each year, according to the WHO, eight to ten million new tuberculosis cases are reported worldwide, and two million people die of the disease. Tuberculosis is second only to AIDS as a cause of death from infectious disease in adults. The vast majority of cases (95%) and deaths (98%) occur in poor countries. The AIDS epidemic (twelve million people with TB are co-infected with HIV) and the growing problem of resistance to tuberculosis drugs (half a million new cases of multi-drug resistant TB annually) have further complicated tuberculosis management.

In terms of research, however, tuberculosis continues to be a neglected disease. Since the discovery of rifampicin forty years ago, there have been no new tuberculosis drugs. Diagnosis still depends largely on sputum microscopy, which is unsuitable for a large number of patients. The efficacy of the BCG vaccine is limited.

The purpose of this manual is to help caregivers take maximum possible advantage of both the existing methods and the rare innovations (rapid cultures, fixed dose combinations, etc.) offering improved diagnosis and treatment.

Despite all efforts, errors may have occurred in the text. Please inform the authors of any errors detected. It is important to remember that, if in doubt, it is the responsibility of the prescribing medical professional to ensure that the doses indicated in this manual conform to the manufacturer's specifications.
The authors would be grateful for any comments or criticisms to ensure that this manual continues to evolve and remains adapted to the reality of the field.

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This manual is also available on the internet at www.msf.org. Medical staff are encouraged to check this website for updates of this edition.

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Abbreviations

AFB	Acid-fast bacilli
ARI	Annual risk of infection
ART	Antiretroviral treatment
BCG	Bacillus Calmette-Guérin
C+	Culture positive for *Mycobacterium tuberculosis*
C–	Culture negative for *Mycobacterium tuberculosis*
CFR	Case fatality ratio
CDC	Centre for Disease Control
CMV	Cytomegalovirus
CPC	Cethylpyrodinium chloride
CXR	Chest X-ray
CSF	Cerebrospinal fluid
DOT	Directly Observed Therapy
DR	Drug resistant
DST	Drug susceptibility tests
E	Ethambutol
EP	Extrapulmonary
EPTB	Extrapulmonary tuberculosis
EPI	Expanded Programme of Immunization
FNAC	Fine needle aspirate cytology
HIV	Human immunodeficiency virus
H	Isoniazid
IU	International units
IUATLD	International Union Against Tuberculosis and Lung Diseases
LP	Lumbar puncture
M+	Positive sputum smear microscopy
M–	Negative sputum smear microscopy
MDR	Multi-drug resistance
PCP	*Pneumocystis carinii* pneumonia
PDR	Mono and Poly drug resistance
PPD	Purified protein derivative (tuberculin skin test)
PTB	Pulmonary tuberculosis

R	Rifampicin
Rx	Treatment
S	Streptomycin
SAT	Self-administered treatment
T	Thioacetazone
TB	Tuberculosis
WHO	World Health Organization
Z	Pyrazinamide
ZN	Ziehl-Neelsen

CHAPTER 1

The disease

1. Epidemiology

1.1. Bacillus characteristics

TB is caused by bacilli belonging to the *Mycobacterium tuberculosis* complex:

– In the majority of cases, TB is due to *Mycobacterium tuberculosis* (Koch's bacillus).

– *M. africanum* may be observed in western Africa (it is often naturally resistant to thioacetazone).

In both of these cases, humans are the only reservoir of bacilli.

– In less than 1% of cases, infection may be due to *M. bovis*, whose reservoir is infected cattle.

– In some regions (Djibouti), TB can be caused by *M. canettii*.

M. tuberculosis multiplies more slowly than the majority of bacteria; this is why TB has a slower evolution than most other bacterial infections.

M. tuberculosis is a strictly aerobic bacteria; it therefore multiplies better in pulmonary tissue (in particular at the apex, where oxygen concentration is higher) than in the deeper organs.

1.2. Transmission

Transmission of the bacillus is human-to-human (except *M. bovis*).

TB is mainly spread by airborne transmission. The source of infection is a patient with pulmonary (or laryngeal) TB who expectorates bacilli. During coughing, speaking, or sneezing, the patient produces tiny infectious droplets; these droplets dry out and remain in the air for several hours. Contamination occurs when these infectious droplets are inhaled. Sunlight and ventilation are effective in decontaminating the environment.

The other modes of contamination are far less common: cutaneous or mucous inoculation of laboratory personnel, or digestive contamination in the event of bovine TB.

The infectiousness of a patient is linked to the quantity of bacilli contained in his/her sputa. Patients with sputum smear-positive microscopy (M+) are by far the most contagious. Those with only culture-positive results (M–, C+) are less contagious. Patients whose sputum smear microscopy and culture are negative (M–, C–) are usually not contagious.

Patients suffering from primo-infection are not contagious. Extra-pulmonary (EP) forms of the disease are only contagious in exceptional circumstances. Children are generally not contagious due to weaker cough mechanics and less sputum production.

It is estimated that a person with TB M+, undiagnosed and untreated, contaminates 10 to 20 people per year (this varies according to lifestyle and environment). Approximately 10% of HIV negative persons infected with the TB bacillus will develop active disease during their lifetime, with the greatest risk in the first two years following infection. About 55% of those patients with active disease have the contagious pulmonary form.

The greatest factors contributing to transmission are the closeness of contact with the infectious source, the duration of exposure, and the bacteriological status of this source.

1.3. Evolution of bacillus in an organism

1.3.1. Primary infection

After contamination, *M. tuberculosis* multiplies slowly, in most cases in the terminal alveoli of the lungs (Ghon focus) and in the lymph nodes of corresponding drainage areas: this represents the primary infection. The Ghon focus and related hilar lymphadenopathy form the primary complex.

In one to two months, due to the action of lymphocytes and macrophages (cellular immunity), lesions will be contained and encapsulated with a central zone of parenchymal necrosis (caseous necrosis). It is at this moment that specific TB immunity appears, and a positive skin reaction to tuberculin is observed. This stage is usually asymptomatic; however, in some rare cases, hypersensitivity reactions may appear (erythema nodosum, phlyctenular conjunctivitis).

In the majority of cases (90% in HIV negative patients), the situation stabilizes at this point, with pulmonary lesions gradually healing.

1.3.2. Active tuberculosis

For the other 10%:
Development is favourable for bacilli and their multiplication continues. Pulmonary and pleural complications may occur. The bacilli spread (usually in small numbers) in the blood from the primary complex throughout the organism, which can then provoke disseminated disease in certain patients (often children): TB meningitis or miliary TB.

Post-primary TB may occur after months or years without clinical signs following primary infection. The emergence of the disease is due to the reactivation of dormant bacilli, which may be in response to a weakening of the immune system (e.g. HIV infection). Post-primary TB generally occurs in adults.
Re-infection of a person who has had a previous primary infection may also lead to active TB. This mechanism is probably frequent in countries with a high risk of infection or in specific settings such as prisons.

It is estimated that half of the cases of active TB appear in the year that follows the infection.

The risk of developing an active TB depends on:

– *Host immune defences:*
  The main factors leading to a weakening of immune response are:
  - Age: small children (risk x 2 in children under 5 and even higher for those under 6 months); people over 60 (risk x 5)
  - Other diseases: clinical AIDS (risk multiplied by 170); HIV infection (risk multiplied by 113); diabetes, cancer (risk multiplied by 4 to 16)
  - Malnutrition
  - Pregnancy
  - Toxic substances and medicines: alcohol, tobacco; corticosteroids, immunosuppressants

– *Bacterial load (number of inhaled bacilli)*, which depends on:
  • Proximity to the infectious source
  • Contagiousness of the source
  • Duration of exposure

1.4. Prognosis and case fatality ratio (CFR)

Pulmonary TB (PTB) is a severe form of the disease. After 5 years without treatment, the outcome of a M+ PTB is as follows:
– 50-60% die (CFR for untreated TB)
– 20-25% are cured (spontaneous cure)
– 20-25% develop chronic M+TB

With adequate treatment, the CFR can fall to less than 5%.

For other forms (EP and M–), the CFR without treatment is estimated in average at approximately 40-50% (these estimates apply to non-HIV patients).

1.5. Modifying factors of TB epidemiology

Four factors can modify TB epidemiology: socioeconomic development, BCG vaccination, TB treatment and HIV infection.

1.5.1. Socioeconomic development

In European countries, the incidence and specific mortality of TB have diminished by 5 to 6% per year since 1850. This progressive improvement dates back to before the era of vaccination and antibiotics and was contemporary with socioeconomic development (improvement of living conditions, nutritional status of populations, etc.).

TB is a disease of the poor: over 95% of cases in developing countries are from poor communities. In industrialised countries, TB generally affects the most disadvantaged social groups.

1.5.2. BCG vaccination

The role of BCG vaccination is controversial. Two notions may be distinguished: the effectiveness of BCG at *an individual level* and the *epidemiological impact* of this vaccination.

Effectiveness of BCG at an individual level

Even though results of controlled surveys are contradictory (efficacy ranging from 0 to 80%), it is acknowledged that BCG, if administered before primary infection (in practice, at birth), confers a protection of 40 to 70% for a period of approximately 10 to 15 years. Protection from the severe forms of TB in children (miliary and meningitis) is estimated at 80%.

Epidemiological impact of vaccination

The analysis of public health statistics of some European countries has shown that BCG vaccination reduces the number of TB cases in vaccinated subjects as compared to those unvaccinated. This reduction measures the direct effect of BCG, i.e. directly conferred protection on those who receive the vaccine.

However, this reduction in the number of observed cases does not have any significant impact on bacillus transmission in a population and thus on the annual risk of infection (ARI).
From an epidemiological point of view, the BCG vaccination is therefore justified by its direct effect (protection against severe forms in children, in particular), but it is not a good tool to reduce transmission.

1.5.3. TB treatment

Since the introduction of anti-TB treatment, a rapid reduction of the ARI has been observed in many industrialised countries, with the infection risk diminishing by approximately 50% every 5 to 7 years during this period. This tendency was observed in countries having a BCG vaccination programme as well as in those without one.

This reduction of the risk of infection is a direct consequence of detection programmes, diagnosis and treatment.

Effective treatment usually substantially reduces or eliminates disease transmission from M+ patients in less than one month after initiation of treatment.

Adequate treatment, because it reduces the infectious period and thus transmission, is the most effective preventive measure against TB.

1.5.4. HIV infection

Immunodeficiency induced by HIV infection is a major risk factor of progression of TB infection up to the stage of active TB.

It is estimated that a subject infected both by HIV and *M. tuberculosis* has a probability of 5 to 10% of developing TB each year, as compared to 0.2% for those infected only with *M. tuberculosis*.

HIV seropositivity rates of 20% in South East Asian countries to 70% in Sub Saharan countries are found in TB patients (2 to 5 times more than in the general population).

Approximately 10% of TB cases in the world (of which 80% are in Africa) are at present associated with HIV.

The impact of AIDS on TB epidemiology can only increase with the spread of the HIV epidemic in Asia, where two-thirds of the world's *M. tuberculosis*-infected population lives.

1.6. Epidemiological indicators

These indicators are used to estimate the TB problem for a given population, define needs and foresee the necessary resources to launch an intervention (see example in Appendix 1).

1.6.1. Annual risk of infection (ARI)

The ARI is a useful indicator, in particular when most of the other indicators are difficult to obtain or are skewed. It permits an estimate of the incidence and the prevalence of TB cases.

This risk expresses the probability that an individual who is not infected with TB bacillus will become so within the course of a year.

This indicator is calculated from the results of a tuberculin survey[1] by measuring, in a younger age group, the percentage of subjects with positive tuberculin skin test in the absence of BCG vaccination. For example, if the percentage of children presenting a positive reaction at the age of 10 is 30%, and, supposing an equivalent infection risk for each year, the ARI would therefore be 3%.

These surveys are difficult to carry out and are complicated by high BCG-vaccine coverage in developing countries. One would therefore more often use reference figures (see table below).

In places where transmission is very high, the ARI can reach values of 3 to 6%.

Estimate of ARI of TB in the world in 1988 (before HIV pandemic)

Region	ARI estimate (%)
Sub-Saharan Africa	2.5
Northern and Western Asia	1.5
Asia	2.0
South America	1.5
Central America and the Caribbean	1.5
Caucasus and eastern Europe	1.5
Industrialised countries	0.5

Source: data reported by Cauthen et al. (1988)

1.6.2. Annual incidence rate of M+ TB cases (iM+)

There is a correlation between the ARI and iM+: approximately 55 new M+ TB cases per 100,000 for each percentage point (1%) of the ARI.

Example: ARI = 1/100 (1%)
1/10 of cases are active TB, of which 55% are M+ forms
iM+ = 1/100 x 1/10 x 55/100 = 55/100,000
iM+ = 55 x ARI (100,000/year)

Studies have shown constant relationships between different morbidity indicators.

[1] Tuberculin surveys for determining ARI are carried out with a specially standardised tuberculin (RT 23, manufactured in Denmark under WHO control).

1.6.3. Prevalence of M+ TB (pM+)

The proportion of a population presenting M+ TB at a specific moment represents approximately double the incidence of these same forms:

pM+ = 2 x iM+/100,000

This prevalence diminishes if effective programmes are running, but may rise in a significant manner in the case of programmes with low cure rates: a high number of patients survive without being cured, and therefore increase the pool of M+ subjects in the population.

1.6.4. Overall prevalence of TB infection

This can be estimated by a tuberculin survey (under the condition that there was no previous BCG vaccination).

It is also possible to estimate the prevalence of active pulmonary forms (by prevalence surveys on a national scale using chest X-rays, sputum smear microscopy and cultures). These surveys are, however, demanding and are rarely done.

All the figures and formulas mentioned above are only valid for countries where the ARI is high.

Note:
The correcting factors for countries with a high prevalence of HIV infection have not, for the moment, been properly established. The risk of developing the disease being higher in HIV patients, the TB incidence for a given ARI is higher. The proportion of M– and EP forms is also higher in HIV patients (60-65%).

1.7. TB in developing countries

In most developing countries, the ARI is over 2% (in almost all industrialised countries, it is below 0.1%) and little or no downward trend is observed. The consequences in terms of morbidity and mortality are major. This situation is worsened by the HIV epidemic.

TB in developing countries is above all an adults' disease (particularly young adults), whereas in industrialised countries it affects the elderly (> 70 years) most of all.

Forms of severe cavitary PTB are more frequent in developing countries; the most probable explanation is delayed diagnosis.

EP localisations are more frequent in developing countries, where they represent approximately 20% of all cases (more where HIV prevalence is high) as compared to 10% in developed countries.

1.8. TB in Eastern Europe and former Soviet Union

The prevalence of drug resistant (DR) TB is greater there than elsewhere. Prisons appear to play an important role in the appearance and diffusion of resistant forms.

The eastern European region has one of the highest level of combined resistance to the 4 most effective anti-TB drugs. For example, nearly 22% of all TB cases in Latvia are multi-drug resistant (MDR), and over one-quarter of all TB cases in Estonia and Russia are resistant to at least one drug.

The situation in central Asia is also very preoccupying: in some regions of Uzbekistan and Kazakhstan over 24% of all TB cases are MDR, over 60% of all TB cases are resistant to at least one drug.

2. Clinical aspects

2.1. Pulmonary TB (PTB)

Certain signs of PTB are quite specific: prolonged cough (> 2 weeks), sputum production and chest pain, while others are less so: weight loss, anorexia, fatigue, moderate fever, and night sweats.
The most characteristic sign is haemoptysis (presence of blood in sputum).

All these signs are variable, and they evolve in a chronic, insidious manner. Thorough questioning of the patient is of utmost importance.

In an endemic area, the diagnosis is to be considered, in practice, for all patients consulting for respiratory symptoms for over 2 weeks who do not respond to non-specific antibacterial treatment.

Advanced forms and complications are not uncommon outside developed countries:
– Respiratory insufficiency due to extension of the lesions
– Massive haemoptysis due to large cavities with hypervascularisation and erosion of vessels
– Empyema (collection of pus in the pleural space)
– Pneumothorax due to the rupture of a cavity in the pleural space

2.2. Differential diagnosis for PTB

– Bronchial carcinoma
– Chronic obstructive bronchitis: in tropical zones, this is a frequent complication of successive and poorly treated bronchopulmonary infections.
– Pulmonary abscesses from common germs (often oropharyngeal flora [staphylococcus] or a mixed bacterial infection).
– Paragonimiasis (pulmonary distomatosis) in certain areas of South-Eastern Asia, western Africa and Latin America. Clinical and radiological symptoms are superimposable on that of TB. The diagnosis can be confirmed by the discovery of the parasite's eggs in the patient's sputum (see Appendix 2.7) or stool, mostly in children.
  In an endemic area, a paragonimiasis smear would therefore systematically be carried out before sputum coloration in TB-suspected cases. The treatment is **praziquantel** PO: 75 mg/kg/day in 3 divided doses for 2 days.
– Other infectious pneumopathies: chlamydia, mycoplasma, Pneumocystis pneumonia (mainly in immunodeficient patients)
– Silicosis, sarcoidosis, berryliosis, melioidosis
– Profound mycosis (cryptococcosis, aspergillosis)
– Pulmonary echinococcosis

2.3. Extrapulmonary (EP) forms

Starting from an initial pulmonary localisation (primary infection), *M. tuberculosis* can spread to the entire organism during a silent phase, generally at the beginning of the infection. Active TB can therefore develop in many other organs, in particular lymph nodes, meninges, vertebrae, joints, genital organs, and kidneys.

These infections present common clinical characteristics: insidious evolution, "cold" lesions often accompanied by deterioration of physical condition, and lack of response to symptomatic or non-specific anti-infectious treatments; they are often isolated, but may be associated with a pulmonary localisation, which should be searched for.

The search for *M. tuberculosis* in smears (urine, pus, ascites fluid, etc.) is almost always negative, but culture helps improve diagnostic yield.

2.3.1. Lymph node TB

Lymph node TB is a frequent pathology in the entire tropical zone, particularly in certain areas of Africa (Senegal, Djibouti), where it represents up to 25% of TB cases, and also in central Asia. In certain areas where TB is highly endemic, 90% of chronic cervical lymph nodes are due to TB. This form is more common in children and in HIV patients.

These are non-inflammatory adenopathies, cold and painless, single or multiple, usually bilateral, evolving in a chronic mode towards softening and fistulisation. Cervical localisation is most frequent, ahead of axillary and mediastinal forms. They are associated with other localisation in 10 to 30% of cases.

Diagnosis is mainly clinical. When the clinical presentation is dubious, the cytology of the lymph node aspirated with a fine needle (see Appendix 2.9) can show in about 60% of cases typical aspect of caseum (granuloma and necrosis). More rarely evidence of *M. tuberculosis* can be found.

Differential diagnosis: ENT cancers, Hodgkin's disease and other lymphosarcoma.

This form of TB is not contagious, does not generally put the patient's life in danger except when it is a complication of a second condition (i.e. HIV disease).

Adenopathies usually disappear in less than 3 months after treatment initiation. Paradoxical reactions may be observed at the beginning of treatment (appearance of abscesses, fistulas or other lymph nodes) and should not lead to a change in treatment.

2.3.2. TB of bones and joints

These forms of TB are mostly found in children, probably because of better vascularisation and oxygenation of osteo-articular structures during growth.

Arthritis: chronic monoarthritis, starting insidiously, with little or no pain, accompanied by joint destruction. The joints most often affected are the hips, knees, elbows, and wrists. Half of these patients have PTB at the same time.

Osteitis (less frequent): it may be a primary osteitis or an osteitis complicating an arthritis. It selectively affects long bones and is occasionally accompanied by cold abscesses. Like arthritis, it is distinguished from common bacterial infections by the contrast of slight symptoms and the extent of destruction detected by radiography.

Spondylodiscitis or Pott's disease: this infection, which can happen at any age, affects vertebrae and disks, bringing about destruction and deformation of the spine. Dorsal localisation is the most frequent. Localised pain may precede the appearance of the first radiological anomalies (destruction of an inter-vertebral disk) by several months. A para-vertebral cold abscess may accompany osteo-articulary lesions; neurological signs may complicate them.

Diagnosis of these osteo-articulary forms is clinical and radiological. Deterioration of physical condition is in favour of TB aetiology.

Treatment is based on the same regimens as for other forms. Certain authors recommend prolonging treatment for up to 9 months (with 7HR). Pott's disease is a severe form of TB that should be treated as a priority. Surgical consultation should be obtained, if possible, for patients with neurological sequelae or an unstable spine lesion.

2.3.3. TB ascites

This is a sign of peritoneal localisation of the infection. The frequency of all types of chronic ascites makes this rather rare form of TB disease a common diagnostic problem in tropical region.

Besides ascites, clinical symptomatology is poor and non-specific: abdominal pain, diarrhoea and an alteration in physical condition. A possible pulmonary or associated genitourinary TB should be searched for.

An ascitic puncture provides the best diagnostic argument:
– a translucent yellow-coloured liquid,
– rich in lymphocytes,
– of an exudative nature: over 30 g of proteins/l (Rivalta test, Appendix 2.6).

The search for *M. tuberculosis* by microscopy is most often negative. Other exudative ascites may be due to carcinoma or bacterial super-infection of a transudate.

2.3.4. Genitourinary TB

Renal localisation is frequent and may be asymptomatic for a lengthy period of time, up to the appearance of urinary signs of extension to the genital tract. Physical condition is preserved most of the time

Diagnosis is suspected in the presence of a micro- or macroscopic haematuria and a "sterile" pyuria by microscopy. The search for *M. tuberculosis* in urinary microscopy is almost always negative, a culture after centrifugation being the only measure to confirm diagnosis.

In women, genital tract contamination can also happen by a haematogenous path. Abdominal pain, leukorrhoea and vaginal bleeding are variable, non-specific signs of this localisation. Extension may be found in the peritoneum and is responsible for ascites. The inaugural manifestation of the disease will often be sterility, which will motivate medical consultation.

In men, genital localisation is secondary to renal localisation. It is manifested most often by cold epididymitis, causing scrotal pain.

2.3.5. TB pleural effusion

The diagnosis of a pleural effusion is based on clinical examination and chest X-rays. This form is more frequent in young adults.

Diagnostic pleural aspiration shows:
– a straw-coloured liquid,
– of exudative nature: proteins ≥ 30 g/l (Rivalta test, Appendix 2.6),
– rich in white cells (1,000-2,500/mm^3), with predominant lymphocytes,
– the search for *M. tuberculosis* by microscopy will most often be negative

In areas of high TB prevalence, these clinical features justify a TB treatment.

2.3.6. TB pericardial effusion

Clinical signs of pericardial effusion: chest pain, shortness of breath, oedema of the lower limbs, and sometimes ascites

The clinical examination shows pericardial friction rub, raised jugular pressure, and tachycardia; the X-ray is a key element for diagnosis and shows an enlarged heart.

Pericardiocentesis may be necessary in the event of acute cardiac impairment. This can only be performed by experienced operators in well-equipped hospitals.

In practice, in areas of high TB prevalence, start a presumptive TB treatment since TB is the most common cause of pericardial effusion.

Differential diagnosis: congestive heart failure.

2.3.7. TB meningitis

In a highly endemic area, TB meningitis generally occurs in children during the first year following primary infection. It is the first form of TB in children below 2 years of age.

Headaches, irritability, fever, and an alteration of physical condition accompany the beginning of the disease, in a variable manner; this is most often progressive. The meningeal syndrome (vomiting, stiff neck, hypotonia in infants, photophobia and headache) is present in most cases. The impairment of the third cranial nerve is classic (oculomotor paralysis).

A lumbar puncture provides the best diagnostic arguments:
– a clear, hyperconcentrated liquid, in which
– proteins are increased (Pandy test, Appendix 2.6): greater than 0.40 g/l,
– glucose is diminished: less than 60 mg/dl,
– containing between 100 and 1,000 white blood cells/ml, of which over 80% are lymphocytes,
– *M. tuberculosis* is rarely found by CSF direct microscopy.

The main differential diagnoses are other clear liquid forms of meningitis (viral and fungal), incompletely treated bacterial meningitis, and meningeal haemorrhages.

Exclude cryptococcal meningitis by CSF microscopy (India ink stain, Appendix 2.8), particularly in HIV patients.

TB meningitis is a medical emergency, and any delay in treatment may result in irreversible neurological sequelae. As soon as the clinical examination and LP results lead to a presumptive diagnosis, treatment must begin.

Treatment is the same as that for other forms: isoniazid, rifampicin and streptomycin easily cross through the meningeal barrier. For this reason, streptomycin is preferred to ethambutol in this indication. Most authors recommend an association with corticoids at the beginning of treatment for severe forms (coma).

2.4. Disseminated or miliary TB

This is a generalised, massive infection characterized by diffusion throughout the organism, (mostly in the lungs) of very small nodulary elements ("millet seeds"). It can occur immediately after primary infection or during reactivation of a latent site.

The classic acute form is mostly found in children and young adults. The beginning, sometimes abrupt, is most often insidious, marked by a progressive alteration of physical condition. The clinical picture is completed in one to two weeks and is characterized by a profoundly altered physical condition, headaches, and constant high fever. Sometimes, discrete dyspnoea and coughing may suggest a pulmonary focus, however lungs are clear on auscultation. A moderate hepatosplenomegaly is occasionally found. Certain forms of miliary TB evolve in a subacute mode over several months.

Confronted with this non-specific clinical picture, septicaemia and particularly typhoid fever might initially be suspected. If there is no possibility of obtaining chest X-rays, certain clinical signs help in making a differential diagnosis: absence of pulse/temperature dissociation, absence of *tuphos*, conserved diuresis, clean, moist tongue, and no toxic facies. Paradoxically, the existence of non-localised bronchitis rales is frequent in typhoid fever. The inefficacy of antibiotics is an argument in favour of miliary TB.

Diagnosis of military TB is confirmed by chest X-ray, which shows small characteristic nodulary infiltration disseminated in both pulmonary fields.

When feasible, fundoscopy would reveal choroidal tubercles.

Sputum smear examination is negative.

Miliary TB in children has a high risk of meningeal involvement (60-70%). A lumbar puncture should therefore be performed in children suspected of having miliary TB.

Blood cell count is slightly modified. The tuberculin skin test is almost always negative.

Like meningitis, miliary TB is a medical emergency.

3. Diagnosis

3.1. Bacteriological examination

Sputum smear microscopy allows a simple, rapid and reliable identification of patients with M+ PTB, but has a low sensitivity. A culture is much more sensitive but requires a more equipped and qualified laboratory.

3.1.1. Sputum collection techniques (Appendix 2.1)

In adults and older children: sputum obtained spontaneously.

In young children and *only in order to perform cultures*:
- Gastric aspiration is sometimes used when sputa cannot be spontaneously expectorated nor induced.
- Sputum induction: inhalation of 5% sterile sodium chloride via a nebulizer induces production of sputum. Due to the risk of bronchospasm, sputum induction must be performed under medical supervision.

Note: if the laboratory exams cannot be performed on site, see Appendix 2.2.

3.1.2. Sputum smear microscopy

The reliability of sputum smear microscopy depends on the quality of sputum collection. Sputum emitted in early morning often shows a higher concentration of *M. tuberculosis*. The reliability of this examination depends also on the proper preparation and interpretation of slides. Quality control checks must be regularly carried out in the laboratory (Appendix 2.11).

It is recommended that 2 successive examinations be done for each patient. Studies in India have shown that, when collection and examination techniques are correctly done, 85% of sputum smear-positive patients are found during the first sputum examination and 10% more during the second; successive, repeated examinations are less and less effective.

Ziehl-Neelsen stain (Appendix 2.3)

Examination technique is based on Acid Fast Bacilli (AFB) characteristics, that is, treated by Ziehl-Neelsen (ZN) stain, it retains a red colour (carbol fuchsin) and resists decolouration by acid and alcohol. The reference method is the ZN hot technique. This method is specific but poorly sensitive compared to culture, particularly in HIV co-infected patients.

The examination can be quantified by using a classification based on the number of identified bacilli per field.

Auramine stain (fluorescence microscopy) (Appendix 2.4)

Auramine stain has the advantage of permitting a more rapid slide interpretation. It is recommended in laboratories with a high workload.

It requires trained, experienced technicians, and an ultraviolet microscope (or, less expensive, a specific device that can be adapted to a regular microscope).

The examination can be quantified by using a classification based on the number of identified bacilli per field.

Concentration techniques

Concentration techniques increase the sensitivity of the sputum smear microscopy. Bleach sedimentation is a useful technique and should be envisaged when competent staff is available and the workload permits (Appendix 2.5).

3.1.3. Culture and drug susceptibility tests

Culture

This method, like microscopy, allows diagnostic confirmation of TB. After humidification, decontamination and centrifugation, samples are cultured in a special medium and then placed in an incubator at 37°C.

Time needed to obtain results:
– Lowenstein-Jensen (LJ) solid medium (standard method): 4 to 6 weeks
– Liquid medium (MGIT): 8 to 14 days
– Microcolonies on thin-layer agar medium (TLA): 7 to 14 days

Advantages of culture:
– It is more sensitive than sputum smear microscopy for detection of paucibacillary PTB: its yield appears to be 20 to 30% higher.
– It allows diagnostic confirmation of some EP forms.
– It allows precise identification of the mycobacterium species involved.
– It allows differentiation between dead and live bacilli (this is important in treatment follow-up).

Disadvantages of culture:
– It is a delicate technique (above all, in terms of decontamination procedures), requiring a highly trained staff, high-quality materials, and a steady supply of water and electricity.
– There is a higher risk of staff contamination, which requires use of biological safety cabinets (Appendix 2.10).
– Time needed to obtain results: delays treatment (especially the standard method).

Cultures should play a bigger role in diagnosis and patients' follow-up due to the limited performances of direct microscopy for:
– Clinically-suspect cases who have already produced 2 sputum smear-negative results, especially HIV+ patients
– Confirmation of failures
– Diagnosis of EP forms
– Evaluation of treatment outcomes in patients who received adapted treatment for drug-resistant TB

New diagnostic tests based on mycobacteriophages may prove to be useful in the future.

Drug susceptibility tests (DST)

It is recommended, whenever possible, that DST be performed when there is a clinical suspicion of resistance and that adapted treatment can be implemented.

The carrying out of DST requires a laboratory highly specialised in *M. tuberculosis* cultures.
The laboratory performing DST should be reliable and subject to external quality assessment by a supranational laboratory; methods used can vary, and DST readings are difficult to interpret.

Rapid methods for cultures and DST are recommended where TB-DR patients are treated. Such methods can give results in about 2 weeks.

3.2. Other diagnostic tools

TB can also be diagnosed with the aid of other techniques that allow a presumptive diagnosis and sometimes confirm pulmonary and EP forms.

3.2.1. Radiography

Pulmonary TB

Chest X-rays are useful for the diagnosis of M– PTB and TB in children.

However several comparative studies have shown that the error rate through under- or over-reading of the film by specialists is around 20%. It is often difficult to detect the difference between cicatricial lesions and active TB. They are rarely conclusive and can only complete the clinical presentation and history to constitute a body of arguments suggestive of TB.

Chest X-rays is not be routinely indicated in M+ patients.

Extrapulmonary TB

X-rays are also valuable tools for the diagnosis of pleural and pericardial effusions, especially at the early stages of the disease when the clinical signs are minimal.

X-rays of the joints and bones typically show important destruction as compared to relatively moderate clinical signs.

Chest X-ray is essential in the diagnosis of miliary TB.

3.2.2. Tuberculin skin test (PPD)

Cutaneous hypersensitivity to tuberculin reflects a delayed hypersensitivity reaction to some *M. tuberculosis* antigens. A positive reaction signifies that an infection has occurred, but it does not determine if the TB is latent or active and is not synonymous with immunity.

The reference technique is a tuberculin skin test at 5 IU of tuberculin (0.1 ml strictly intradermally, on the internal (volar) surface of the forearm).

Its reading is quantitative: measured in millimetres, in the length of skin induration, in the longest axis (not the erythematous area). The test is read 72 hours after injection.

Techniques that do not allow a quantitative reading (cuti, stamp, ring, etc.) should not be used.

BCG induces a state of hypersensitivity: the average diameter is 10 mm, with extremes ranging from 4 to 20 mm. This vaccine reaction has a tendency to subside and then disappear in 5 to 10 years.

A TB infection is suspected in vaccinated subjects in the following cases:
– Phlyctenular PPD
– Recent increase of over 10 mm in the reaction, without revaccination
– Persistence of a strong reaction over 10 years after BCG
– High intensity induration well beyond 72 hours

In practice PPD has little value as a diagnostic tool when ARI and BCG vaccine coverage are high. It can only be used as an element among a body of arguments to establish a clinical score in children.

Quantitative reading can give diagnostic orientation but not confirmation.

A reaction that appears several minutes or several hours after injection (occasionally even after 24 hours) but which disappears on the day after its appearance is of no value.

A highly positive or phlyctenular reaction (induration diameter over 20 mm) should be considered as an argument in favour of active TB, but insufficient in itself for deciding on treatment. A mild topical corticosteroid (1% hydrocortisone) may be considered in severe local reactions that are at risk for ulceration.

Negative reactions in patients that previously presented positive reactions signify a loss of hypersensitivity. It may be observed:

– Temporally:
  • during viral (influenza, measles) or bacterial (whooping cough) infections,
  • at the start of the evolution of TB meningitis or miliary TB,
  • in patients in poor general condition (malnutrition),
  • during immunosuppressive treatment (corticoids).
– Definitively:
  • natural extinction of post-vaccination reaction, observed from the fifth year that follows BCG,
  • weak immune response in very elderly persons,
  • anergic disease: AIDS, haemopathies, sarcoidosis.

It should be noted that approximately 30% of children with active TB have negative or doubtful PPD when diagnosed.

3.2.3. Anatomopathological examination

Anatomopathological examination only concerns EP forms. Biopsies do not have a place in routine practice, but the cytology of the lymph nodes aspirate (FNAC) can help to confirm the diagnosis of TB when clinical presentation is not typical (Appendix 2.9). Specific granulomatous tissue, the presence of giant Langhans' cells, and/or caseous necrosis confirm TB.

3.2.4. Other biological examinations

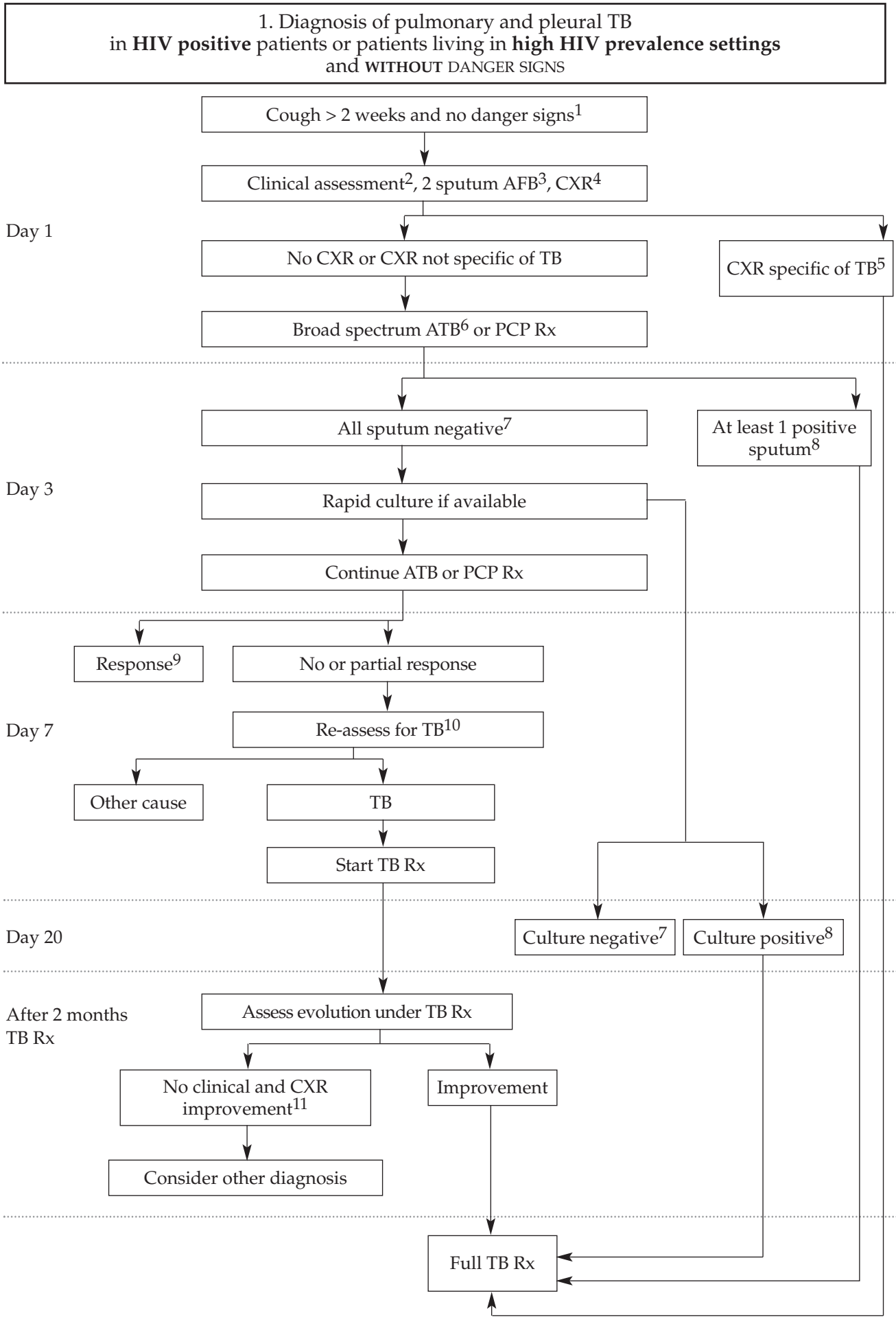
Complete blood count is little or not at all modified.
A neutrophil polynucleosis would instead indicate a common germ infection.
Sedimentation rate is almost always higher but this examination has no specificity.

Surrogate markers such as the cell count (lympocytes), protein (Pandy and Rivalta tests, Appendix 2.6), can provide useful indication in ascites, pleural effusion and meningitis.

There exist rapid serological tests for serological diagnosis of TB, but they are so far not very reliable in diagnosing TB disease and should not be used.

3.3. Diagnostic algorithms

See following pages.



See notes next page

1. Danger signs: respiratory rate > 30/min and fever > 39°C and/or pulse rate > 120/min and/or unable to walk.
2. Clinical assessment:
   HIV status? Cotrimoxazole prophylaxis?

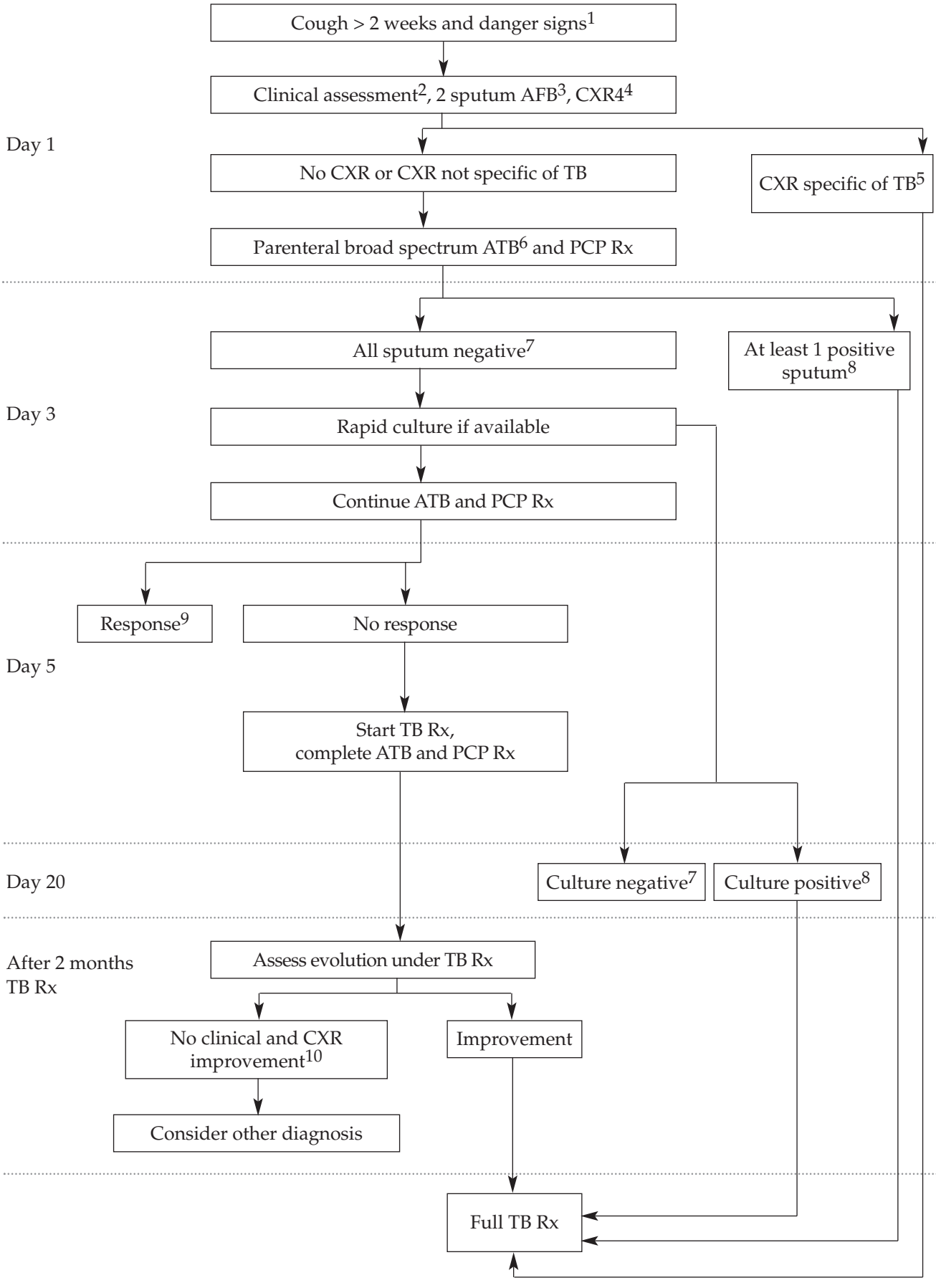
	TB	PCP (HIV+)	Bacterial
Typical clinical signs	Productive cough, weight loss, purulent sputum, haemoptysis, pleuritic chest pain	Dry cough Dyspnoea ++	Acute onset Fever

3. Two sputum: 1 on the spot, 1 next morning.
4. Chest X-Ray:

	TB	PCP (HIV+)	Bacterial
Typical CXR	Upper lobe infiltrates, cavitation, hilar adenopathies, pleural effusion (straw coloured liquid aspirate), miliary	Bilateral diffuse shadowing	Lobar consolidation

5. When chest X-ray is "specific of TB" (miliary or pleural effusion with straw coloured liquid aspirate), TB Rx should be initiated immediately.
6. E.g. amoxicillin for 7 days (no fluoroquinolones)
7. No definite conclusion can be drawn from negative bacteriological examinations.
8. Bacteriological confirmation at any point in time in the algorithm implies full TB Rx
9. Clinical response to broad spectrum antibiotic does not rule out TB. Patient should be informed to consult if symptoms recur.
10. – If patient is clinically stable: review X-ray for signs suggestive of TB. Do X-ray if not done at Day 1. According to clinical signs, response to previous treatment and X-ray, consider PCP or TB Rx. Repeat 2 sputum for AFB.
    – If patient is clinically deteriorating: refer to algorithm 2.
11. In the absence of any clinical improvement (no weight gain; cough, pain) AND no improvement on CXR after 2 months of a well conducted TB Rx, diagnosis and treatment should be reconsidered.

2. Diagnosis of pulmonary and pleural TB in **HIV positive** patients or patients living in **high HIV prevalence settings** and **WITH** DANGER SIGNS



See notes next page

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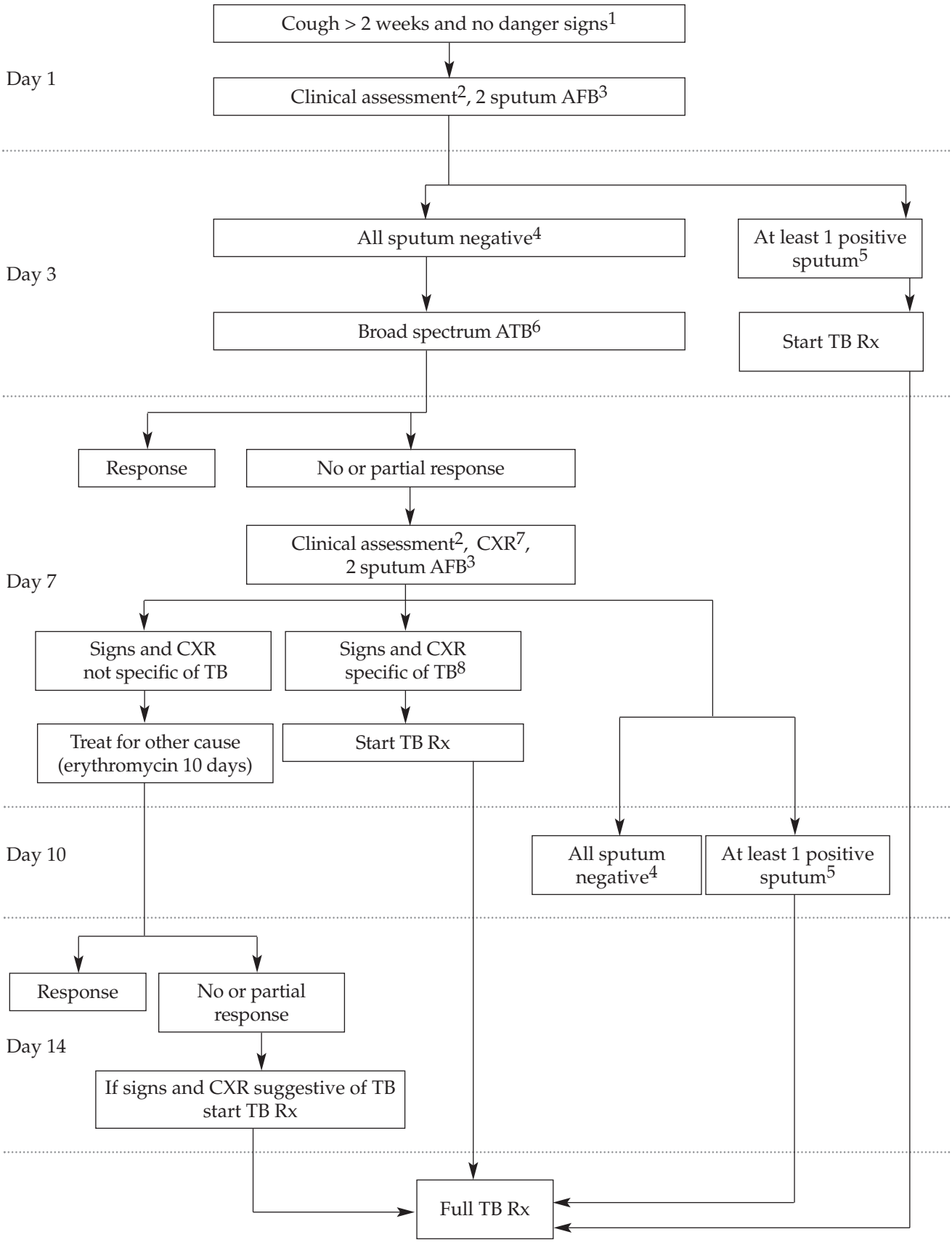
8. Bacteriological confirmation at any point in time in the algorithm implies full TB Rx
9. Clinical response to broad spectrum antibiotic does not rule out TB. Patient should be informed to consult if symptoms recur.
10. In the absence of any clinical improvement (no weight gain; cough, pain) AND no improvement on CXR after 2 months of a well conducted TB Rx, diagnosis and treatment should be reconsidered.

3. Diagnosis of pulmonary and pleural TB in **HIV negative** patients or patients living in **low HIV prevalence settings** and **WITHOUT** DANGER SIGNS



See notes next page

1. Danger signs: respiratory rate > 30/min and fever > 39°C or pulse rate > 120/min or unable to walk.
2. Clinical assessment:
   HIV status?

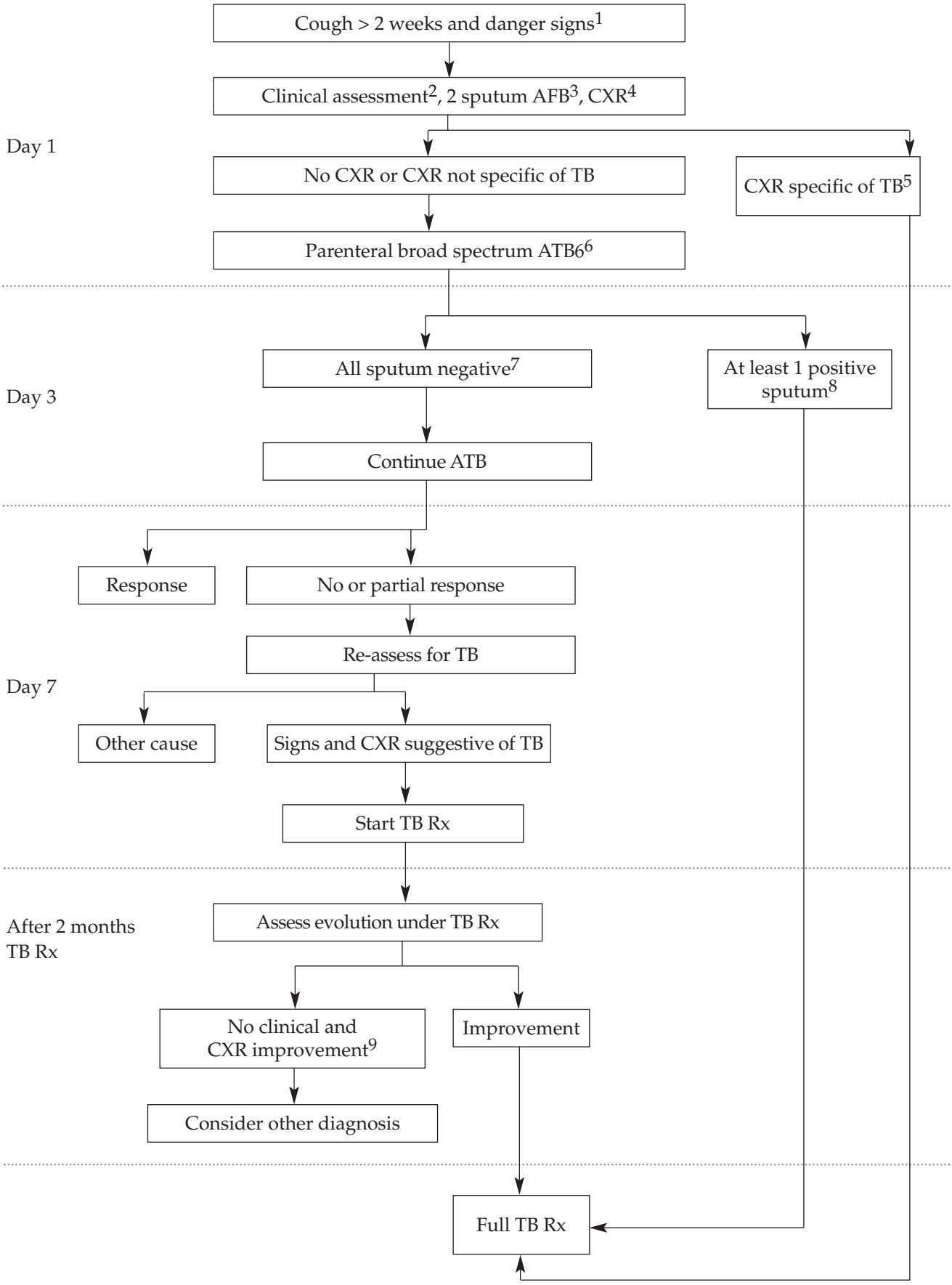
	TB	Bacterial
Typical clinical signs	Productive cough, weight loss, purulent sputum, haemoptysis, pleuritic chest pain	Acute onset Fever

3. Two sputum: 1 on the spot, 1 next morning.
4. No definite conclusion can be drawn from negative microscopy.
5. Microscopic confirmation at any point of time in the algorithm implies full TB Rx.
6. E.g. amoxicillin for 7 days (no fluoroquinolones).
7. Chest X-Ray:

	TB	Bacterial
Typical CXR	Upper lobe infiltrates, cavitation, hilar adenopathies, pleural effusion (straw coloured liquid aspirate), miliary	Lobar consolidation

8. When Chest X-ray is specific enough of TB (miliary, cavitation, pleural effusion with straw coloured aspirate) TB Rx should be initiated without waiting for the result of the 2nd set of sputum microscopy.

4. Diagnosis of pulmonary and pleural TB in **HIV negative** patients or patients living in **low HIV prevalence settings** and **WITH** DANGER SIGNS



See notes next page

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2. Clinical assessment:
   HIV status?

	TB	Bacterial
Typical clinical signs	Productive cough, weight loss, purulent sputum, haemoptysis, pleuritic chest pain	Acute onset Fever

3. Two sputum: 1 on the spot, 1 next morning.
4. Chest X-Ray:

	TB	Bacterial
Typical CXR	Upper lobe infiltrates, cavitation, hilar adenopathies, pleural effusion (straw coloured liquid aspirate), miliary	Lobar consolidation

5. When chest X-ray is "specific" of TB (military, cavitation, pleural effusion with straw coloured liquid aspirate), TB Rx should be initiated without delay.
6. E.g. ceftriaxone for 7 days.
7. No definite conclusion can be drawn from negative microscopy.
8. Microscopic confirmation at any point in time in the algorithm implies full TB Rx
9. In the absence of any clinical improvement (no weight gain; cough, pain) AND no improvement on CXR after 2 months of a well conducted TB Rx, diagnosis and treatment should be reconsidered.

4. Case definitions

4.1. Suspected case of pulmonary TB

Any patient who presents with the following signs:
– Cough lasting over two weeks
– Sputum production
– Weight loss

The fact that a cough has lasted for more than two weeks is the most important sign and the one that should be taken into account, first and foremost, for detection.

This definition designates patients for whom bacteriological examinations would be carried out. If it were too vague (too sensitive), the laboratory would be overloaded with examination requests and, inversely, if it were too specific, detection efficiency would be inadequate.

This definition serves as a basis for training medical personnel in charge of consultations.

For EP forms, symptoms depend on the site of the disease.

4.2. Proven case of TB

A proven case of TB corresponds to a bacteriological definition: presence of *M. tuberculosis* in sputum smear microscopy or culture.

4.3. TB case

A TB case is a patient that has been diagnosed as such by a clinician, whether the diagnosis has been confirmed bacteriologically or not.

The elements necessary for correctly defining a TB case are:
– The bacteriological status
– The site of the disease
– The history of antituberculous treatment

These case definitions have been designed in order to standardise treatment and evaluation.

4.3.1. Bacteriological status and site of the disease

Smear-positive pulmonary TB (M+ or **PTBM+)**

Patient with at least one sputum smear-positive sample

Smear-negative pulmonary TB (M– or **PTBM–)**

Pulmonary TB that does not correspond to the definition of PTBM+[2]
AND
for whom a clinician prescribes anti-TB treatment.

Extra-pulmonary TB (EPTB)

Patient with clinical signs corresponding to extra-pulmonary active tuberculosis OR patient with at least one culture-positive non-pulmonary sample
AND
for whom a clinician prescribes anti-TB treatment.

Sputum smear microscopy should always be done and culture when possible. Patients presenting with TB pleural effusion, miliary TB or mediastinal lymphadenopathy without evidence of parenchymal localization are classified in this category.

Note: any patient presenting with PTBM+ and an EP form at the same time is considered an M+ case for recording purposes.

4.3.2. Treatment history

Patients who have taken anti-TB drugs for one month or more in the past have a higher risk of developing drug resistance. It is therefore important to question patients closely about their previous history before beginning treatment.

New case

Patient who has never taken anti-TB drugs for over one month in the past 5 years.

Re-treatment

Patients who received at least one month TB treatment in the 5 past years and return with a diagnosis of TB.

This group includes:

– *Relapse:*
  Patient who received at least one month TB treatment in the 5 past years, who was classified as "cured" or "treatment completed" but who returns with the diagnosis of TB M+, M– or EP.

– *Failure:*
  Any patient who presents smear positive sputum at 4-5 months of treatment or thereafter
  or
  Any patient who presents positive culture at 4-5 months of treatment or thereafter, regardless of smear status
  or
  Patient initially M– or EP with no significant clinical improvement and no significant gain of weight after 4-5 months of treatment and for whom the diagnosis of failure is established by a clinician
  or
  Patient initially M– or EP who presents smear positive sputum at the end of the intensive phase

[2] For example: patient with sputum smear-negative samples whose culture is positive OR patient with two sets - taken at least one week apart - of at least two sputum smear-negative samples, and no response to a broad-spectrum antibiotic treatment (see algorithms, pages 32 to 39).

– *Return after default (or treatment after interruption):*
  Patient who interrupts treatment for over 2 months and who returns with the diagnosis of TB M+, M– or EP
– *Others:*
  Patients who cannot be included in one of the above categories; e.g., patients who have previously been treated via an erratic or unknown TB regimen

Transferred in

Patient who began treatment and had been registered in another TB centre, and was then referred during treatment.

5. TB and HIV

TB is a leading cause of HIV-related morbidity and mortality and is one of the main opportunistic diseases. The principles of TB diagnosis are the same regardless of HIV status, though areas with high rates of TB-HIV co-infection face an increased proportion of M– and EP TB.

According to the WHO clinical staging of HIV/AIDS, HIV patients with pulmonary TB are in clinical stage 3; HIV patients with extra-pulmonary TB are in clinical stage 4.

5.1. Signs and symptoms of TB in HIV patients

In the early stages of HIV infection, when the immune system functions relatively normally, the clinical signs of TB are similar to those in HIV-negative individuals.

As the immune system deteriorates in later stages of the disease, the patterns of TB presentation becomes increasingly atypical, with M–, disseminated, and EP forms becoming more common. These cases are more difficult to diagnose and have a higher fatality rate than M+ cases.

In adults, the most common EP forms are lymphadenopathy, pleural effusion, pericarditis, miliary TB, and meningitis. TB meningitis, miliary, and diffuse lymphadenopathy are the leading EP forms in children.

Pulmonary TB patients with HIV tend to experience more fever and weight loss compared to those who are seronegative, but suffer less coughing and haemoptysis due to lesser inflammation and cavity formation.

5.2. Diagnosis of TB in HIV patients

5.2.1. Bacteriological examination

Sputum smear examination still remains useful means of diagnosis and should be performed systematically on all HIV patients in countries with a high prevalence of TB. Patients with heavy immune deficiency will provide smear-positive sputum less often, even in the presence of a high bacillary load. Smears should be repeated, if initially negative, when the suspicion of TB remains high.

Concentration technique (Appendix 2.5) can augment the sensitivity of sputum microscopy.

Auramine staining (Appendix 2.4) can allow a quicker reading of the slides. This can significantly contribute to diminishing the workload in the laboratory and thus improving the quality of readings.

Consistently negative smears should alert one to the presence of other pathology: pneumocystosis, viral (CMV), fungal (candida, cryptococcus) or mixed bacterial pneumonia, and pulmonary Kaposi's sarcoma.

5.2.2. Radiography

In many programmes, chest X-rays are obtained only if 3 sputum smears are negative or produce only a single positive slide.

Chest radiography alone is not sensitive or specific enough to establish a diagnosis of TB. The dictum that no single chest X-ray pattern is indicative of active TB is particularly true in the presence of HIV co-infection: infiltrate, especially in advanced immunodeficiency, tends to be more diffuse and located in the lower lung zones; the X-ray may even appear normal.

5.2.3. Tuberculin skin test (PPD)

HIV-infected individuals are considered to have a positive test when skin induration is measured as greater than 5 mm in the longest axis.

False negatives are seen for example in cases of advanced immunodeficiency.

False positives may result from a prior BCG vaccination or when the patient is infected with a non-tuberculosis form of mycobacterium.

Therefore, the diagnosis of TB in sputum smear-negative patients should follow a simple algorithm (pages 32 to 39), adapted to the conditions and possibilities of the context.

5.2.4. Culture and rapid tests

Due to low sensitivity of smear microscopy, rapid culture techniques should be integrated to laboratory services in areas with high HIV and TB co-infection.

*Difference in TB presentation in HIV**

	Stage of HIV infection	
	Early	Late
Clinical signs	Similar to typical post-primary TB	Similar to primary TB infection
Smear results	Usually positive	Often negative
Radiograph pattern	Cavitation, upper lobe lesions, bilateral, fibrosis	Interstitial infiltrate, few cavities, or even “normal”

** Adapted from “TB and HIV”, WHO, 2005.*

5.2.5. Notes on distinguishing TB from other processes in HIV patients

TB lymphadenopathy

Lymphadenopathy is relatively common in HIV patients.
Persistent generalized lymphadenopathy (PGL) is the most common cause of adenopathy (up to 50% of HIV patients). In PGL, lymph nodes are symmetrical, not tender, and often involve posterior cervical or epitrochlear nodes.
The clinical presentation of lymph node TB (see page 23) in HIV patients is often atypical. Fine-needle aspiration of lymph nodes may help confirm the diagnosis.
Other causes of lymphadenopathy can be lymphoma, carcinomatous metastases or Kaposi's sarcoma.

Wasting

Disseminated TB may be under-diagnosed in HIV as it may be confused with the severe wasting seen in advanced stage of HIV infection.
Chest X-rays can usually confirm miliary TB.
Other diseases that have features similar to miliary TB include disseminated carcinoma, atypical mycobacteria and other endemic infections.

Serous effusions

Pleural
TB remains the most likely cause of an exudative pleural effusion in young adults. Serous effusions are more common in HIV patients.
Alternative diagnoses, such as malignancy, post-pneumonic effusions, pulmonary embolism and amoebic liver abscess, have to be considered.
Obtaining pleural fluid is essential.

Pericardial
In the presence of a pericardial effusion (in high TB-HIV prevalence areas), TB is often the most likely treatable cause and it is safer to start a full course of anti-TB treatment than risk pericardiocentesis.
Other diseases leading to pericardial effusion include uraemia, heart or liver failure, malignancy, hypothyroidism, bacterial infection, and various other inflammatory illnesses.

Meningitis

Signs and symptoms of TB meningitis are similar to other forms of meningitis that may occur in HIV patients, though TB meningitis is usually of insidious onset when compared to the usual bacterial forms.
Lumbar puncture is normally safe in suspected TB meningitis, though increased intra-cerebral pressure (i.e. by fundoscopy) should be ruled out.
CSF usually has the same characteristics as in HIV-negative patients (low glucose, high protein (Pandy+), increased white cells count with lymphocyte predominance), but may also be unaltered. Perform India ink examination to rule out cryptococcosis.
Finding TB bacilli in a smear of CSF fluid is rare.

Pneumonia

Infiltrative processes of the lungs in HIV patients have multiple possible aetiologies:
– Bacterial infections are more common at all stages of HIV infection. The most frequently encountered organism, as in non-HIV patients, is *S. pneumoniae*.
– *Pneumocystis carinii* pneumonia (PCP) has many characteristics in common with TB (insidious onset, persistent cough, fever) but tends to occur in the latter stages of HIV (T-cells < 200), imparts a greater degree of dyspnoea, rarely produces effusions, and is not usually accompanied by haemoptysis. Cotrimoxazole is used for the prophylaxis and the treatment of PCP.
– Pulmonary Kaposi's sarcoma can resemble TB, with slow-onset cough, fever, haemoptysis, night sweats, and weight loss. It is a disease of late-stage HIV and, in most cases, is preceded or accompanied by lesions involving skin and mucus membranes.

Less common:
– Cryptococcus (and other fungi) pulmonary infections may resemble TB. Cryptococci may be found in the sputa.
– Nocardiosis pulmonary infection: on direct smear, nocardia are weakly acid-fast, similar in appearance to mycobacteria (although they are branching filamentous bacilli, particularly on Gram staining).

Pulmonary processes in HIV

	HIV stage	Onset	Cough/Sputum	Dyspnoea	Chest X-rays
TB	Any	Chronic; may appear only as wasting in late HIV	*Early HIV*: productive cough; SSM+ *Late HIV*: scanty bacilli or SSM–	Not predominant	*Early HIV*: typical *Late HIV*: any presentation; also hilar adenopathy
PCP	Typically late (T-cells < 200)	Typically insidious	Dry, non-productive cough	Prominent in severe disease	Normal to interstitial infiltrates; pneumothorax; effusions rare
Typical bacteria	Any	Acute	Cough +	May predominate	Lobar consolidation; less typical late
Mycoses	Late (T-cells < 100)	Subacute or insidious	Possible haemoptysis; cysts or hyphae in sputum microscopy	May be prominent	Focal or diffuse interstitial pattern
Kaposi's sarcoma	Any	Insidious; 80% have skin lesions first	Cough not predominant; possible haemoptysis	Usually predominant	Bilateral diffuse nodular infiltrate

5.3. Diagnosis of HIV in TB patients

The diagnosis of HIV relies on serology testing. In areas where there is a high prevalence of HIV (> 1% in pregnant women), HIV testing should be systematically offered to all TB patients, including children.

Pre-test counselling must be available to all patients so that they understand what the implications of the results might be and so make an informed choice on whether or not to have the test. **HIV testing of TB patients must not, in any case, be compulsory**.
Patients should be counselled on behaviour risks and methods to prevent transmitting or acquiring the infection.
After the test, patients who are diagnosed as HIV positive should receive relevant medical care.

One must remember that there is a period of 6 to 12 weeks during which a newly infected patient will not yet have detectable antibodies (window period), so the HIV test can be negative and may need to be repeated at a later date.

6. TB in children

In countries with a high TB prevalence, first contact with TB bacilli usually happens during early childhood.

6.1. Specificities of TB in children

The risk of rapid progression towards an active form of the disease varies according to age:

– It is very high in infants (< 6 months); approximately 50% of infected children in this age group develop active TB, most often meningeal or miliary forms which are severe. Development of active disease remains relatively high up to the age of 3 to 4 years.
– From the age of 3 or 4 years to adolescence, this progression is uncommon. Generally, non-cavitary pulmonary forms are observed, little or no sputum production (M–); most patients recover spontaneously and then occasionally reactivate at puberty. EP (notably lymphadenopathic and osteoarticular) and disseminated forms are frequent.

Malnutrition, measles, whooping cough, HIV infections and many other morbid conditions diminish the body's defences and may be responsible for progression towards active TB.

Smear positive TB is rare in children. It represents 10% of all TB observed in the 0 to 14 age group, or 2 to 3% of all M+ cases.
Tuberculosis in children is characterized by the following:
– Children play a minor role in transmission;
– Diagnosis in children is often difficult, especially when limited means are available.

Due to lack of effective diagnostic tools TB is frequently under-diagnosed in children. It is considered that children represent about 10 to 20% of all TB cases in a population.
Despite the lack of good tools to diagnose TB, every effort has to be made to diagnose and treat children with TB are treated.

6.2. Indicative signs

TB would be suspected in children in the following situations:

– Cough > 2 weeks

– Fever > one week, without evident cause
– Pleural effusion
– Break in weight curve for over 4 weeks in the absence of a notable reduction in the provision of food, or persistent malnutrition after one month of well-supervised nutritional care, in the absence of other known causes
– Persistent pneumopathy after two different, well-monitored antibiotic treatments
– Meningeal signs, often in a sub-acute context, i.e. headaches, irritability progressively evolving towards disorders of consciousness (lethargy, etc.), occasionally associated with a focal neurological deficit. Approximately 75% of children with TB of the central nervous system have an associated pulmonary localization. Miliary TB is quite often found in this case;
– Stiffness and vertebral deformation, subacute arthritis in general, occasionally associated with fistulisation;
– One or more lymph node(s), firm or soft, painless, and occasionally abscessed.

Given the wide range of possible signs and their absence of specificity, differential diagnoses are numerous and cannot be detailed in this guide.

Young children are almost always infected by close familial contact. Existence of a known case of sputum positive TB patient in the immediate circle of a child is an important argument in favour of diagnosis.

6.3. Confirmation of diagnosis

Bacteriological confirmation of the diagnosis (sputum smear microscopy or culture) is rarely possible because it is difficult to obtain sputum from children.

Chest X-rays may be used to argue the case for deciding whether or not to treat a child, but is rarely absolutely conclusive.

In practice, the diagnosis is based on paediatric scores calculated using patient's history and clinical examination. A high score (7 or above) implies a positive diagnosis to decide to treat the child. These scores are valuable tools because they require the use of a systematic diagnostic approach. However, their performance (sensitivity, specificity, and positive predictive value) has not been properly validated. The lack of validation is even more significant in areas of high HIV prevalence due to reduced specificity of clinical features and reduced sensitivity of tuberculin test.
The most commonly used score chart is the Keith Edwards (see below).

6.4. Paediatric scores

	0	1	3	Score
Duration of the disease	less than two weeks	two-four weeks	more than four weeks	
Nutritional status	> 80% of weight for height	between 70 and 80%	less than 70%	
Family contact with TB patient	none	reported by family	contact with confirmed M+ subject	
			Total (1) =	

Positive tuberculin skin test	3
Painless adenopathies in one or several regions, with fistulisation	3
Night sweats, unexplained fever	2
Malnutrition, with no improvement after four weeks of re-nutrition	3
Presence of vertebral deformation	4
Arthritis with bone deformation, of sub-acute character, with or without fistulisation	3
Unexplained abdominal mass or ascites	3
Neurological disorders: change in behaviour, convulsions, coma, etc.	3
Total (2) =	

(Adapted from Keith Edwards, The diagnosis of childhood tuberculosis. 1987)

Total 1 + 2 = _____

A score greater than or equal to 7 is highly suggestive of TB.

TB diagnosis in children is most often presumptive. This diagnosis would be more probable if clinical evaluations were done systematically. After careful clinical examination and investigation, a decision has to be made whether or not to start a full TB treatment. A treatment trial should be avoided.

TB treatment in children follows the usual TB regimens as for adults. Dosage has to be adapted according to the weight.

7. Resistance to anti-TB drugs

Resistance to anti-TB drugs emerged at almost the time as the discovery of streptomycin. The prevalence of drug resistant (DR) strains has increased since the early 1990s. It has become a major problem in some countries.

7.1. Definitions

7.1.1. Natural resistance

Natural resistance concerns bacilli that are naturally resistant to an individual TB drug due to spontaneous genetic mutation.
Rates of resistance-inducing tubercular DNA mutations are different for each of the first-line drugs: one in every 1,000,000 TB bacilli in a typical focus of infection is naturally resistant to isoniazid and one in every 100,000,000 is resistant to rifampicin.
The risk of mutations conferring resistance to both drugs (isoniazid and rifampicin) resulting in multi-drug-resistant TB (MDR-TB) is extremely rare: i.e. one out of every 10^{14} bacilli is naturally MDR. Typically, a cavity with a 2-cm diameter contains approximately 10,000,000 bacilli.
In some smear-negative and EP TB, the number of bacilli is small enough to preclude the chance appearance of drug resistance.
Certain mycobacterial species are consistently resistant to individual drugs: *M. africanum* is naturally resistant to thioacetazone, and *M. bovis* is naturally resistant to pyrazinamide.

7.1.2. Primary resistance

When resistance is found in a patient who has never before received anti-TB treatment, the patient is said to have primary resistance, having been infected by someone harbouring a strain of TB already resistant to TB medication (i.e. from a patient who has secondary resistance, see below).
The most frequent primary resistances affect the most widely distributed drugs, i.e. isoniazid and streptomycin.
Increased rates of primary resistance typically occur when secondary drug resistance is already significant and conditions favour TB transmission (overcrowding, poor case-finding or improper patient isolation).

7.1.3. Secondary resistance

Secondary resistance develops in patients during the course of TB treatment and is entirely manmade.
High rates of secondary resistance are often found in countries where treatment regimens are inadequate or suffered economic and social disruption leading to interrupted drug supplies.

7.1.4. Initial resistance

Resistance to one or more anti-TB drugs in a new case. This might be a primary resistance or an undiagnosed secondary resistance.

7.1.5. Multi-drug resistance (MDR)

A multi-drug-resistant strain is defined as a strain resistant (at least) to isoniazid and rifampicin.
It can occur primarily (a patient infected by someone with MDR-TB) or secondarily (poor prior therapy). This grave problem was brought to attention in the early 1990s following the observation of several hospital-acquired outbreaks of MDR-TB, particularly among patients with HIV-related illnesses. In most cases, resistance followed erratic treatments.
MDR is currently a major problem in the former Soviet Union (Russia, the Baltic states, the Caucasus, central Asia, etc.), China, and the Dominican Republic, among others. In many countries, prisons are also considered to be at risk of high prevalence of MDR-TB.
M+ TB patients with resistant bacilli are as contagious as those infected by sensitive bacilli.

7.1.6. Mono or poly-drug resistance (PDR)

Resistance to at least isoniazid or rifampicin but not both simultaneously. These patterns of resistance require adapted regimen in order to prevent possible evolution to MDR-TB under standard regimen (resistance amplification).

7.1.7. Ultra-resistance (XDR = extensive drug resistance)

A strain is considered extremely resistant if it is multi-drug resistant and also resistant to at least fluoroquinolones and one second-line injectable drug (kanamycin, amikacin or capreomycin).
The frequency of this potentially incurable resistance is poorly documented as few laboratories are capable of carrying out second-line DST; however very alarming figures have been published (South Africa).

7.2. Main causes leading to development of resistance

– Use of monotherapy, for whatever reason: inadequate prescriptions, shortages of drugs, self-medication. Resistant bacteria will continue to grow, soon replacing the sensitive bacterial population. From this springs the first absolute rule: **never administer monotherapy**.
– Use of ineffective antibiotic combinations during initial phase: e.g., isoniazid and ethambutol, isoniazid and thioacetazone, or only isoniazid and rifampicin in areas with high primary resistance to isoniazid.

– The "adding syndrome", which consists of adding a single new antibiotic to a patient already under a treatment regimen that appears to be failing. This is equivalent to administering monotherapy, creating a second absolute rule: **never add a single anti-TB drug to a failing regimen**.
– Treatment that is not properly adhered to: this may be due to the patient and/or lack of support from healthcare staff.
– Use of drugs of doubtful quality (e.g. FDC whose bioavailability is not satisfactory).

CHAPTER 2

Treatment

1. Principles

An active tuberculous lesion contains at least four distinct *M. tuberculosis* populations:
- Actively multiplying bacilli in open cavities that are responsible for contagiosity
- Slowly multiplying bacilli in acidic inflammatory tissue
- Sporadically multiplying bacilli in tissues
- Dormant bacilli in solid lesions

Each anti-TB drug has a specific action on one or more of these bacillary populations but none on dormant bacilli.
The combination of several anti-TB drugs is necessary for treating the disease and avoiding the emergence of resistance.
A therapeutic regimen defines the combination of drugs used and the length of use of each drug.

From a pharmacological point of view, regimens are assessed according to the following criteria:
- Capacity to rapidly reduce actively multiplying bacillus populations, for rendering sputum smear negative and the patient non-contagious
- Capacity to completely destroy the three multiplying bacillus populations
- Capacity to prevent development of drug resistance
- Importance of adverse effects

2. First-line anti-TB drugs

The five main anti-TB drugs in use are the following:
– Isoniazid and rifampicin, the two main bactericides
– Streptomycin and pyrazinamide, which have complementary bactericidal action
– Ethambutol, a bacteriostatic drug that is associated with bactericides in order to avoid the emergence of resistance

These medicines are designated by their abbreviations (international codification):

H	=	isoniazid
R	=	rifampicin
S	=	streptomycin
Z	=	pyrazinamide
E	=	ethambutol

A number indicates the length of treatment in months. For example, 2 SHRZ signifies 2 months of quadruple association S + H + R + Z.

Two (or three or four) drugs placed in brackets like 2 (HRZE)/4 (HR) means that fixed dose combinations (FDC) are used.

In intermittent treatments, a number placed after a letter (e.g. H3R3) refers to the number of times the drug is taken per week.

To ensure the quality on anti-TB drugs used, it is essential to check their origin. See Appendix 3 for the list of anti-TB drugs prequalified by the WHO. As this list is regularly updated, also refer to the web site http://apps.who.int/prequal/.

2.1. Oral drugs

2.1.1. Isoniazid (H)

Isoniazid is the most potent bactericide against rapidly multiplying bacilli. It comes in 100 mg, 300 mg tablets, in FDC tablets and in 50 mg/5 ml syrup.

Dosage and administration

Children < 30 kg: 10 mg/kg/day; maximum 300 mg/day
Children ≥ 30 kg and adults[1]: 5 mg/kg/day; maximum 300 mg/day

Isoniazid is prescribed as a single daily dose, since it is more important to obtain a high serum peak than to maintain a medium concentration for obtaining bacillus inhibition.

Aluminium hydroxide should not be taken with isoniazid because it impairs its absorption.

[1] Adult doses should be used for children older than 10-13 years. For simplification the cut-off has been set at 30 kg.

Adverse effects

When these doses are respected, adverse effects are rare.

During the first weeks of treatment, hypersensitivity reactions (fever, skin rash) may occasionally occur.

The most common adverse effect is peripheral neuropathy. It begins with paraesthesia, and prickling/burning sensations in the feet and hands. It may be accompanied by anaesthesia, loss of sensation in joints, reduction of muscular strength, and/or elimination of Achilles tendon and knee-jerk reflexes.
Isoniazid-related neurotoxicity is prevented with a low dose (6 to 10 mg daily) of pyridoxine (vitamin B6) to patients at risk (malnourished, alcoholic, HIV, pregnant women, and diabetic patients). Giving higher doses of pyridoxine for prevention should be avoided because this may reduce the antibacterial activity of isoniazid.
If neuropathies appear, they should be treated with pyridoxine, 100 to 200 mg/day, without interrupting isoniazid treatment.

Other adverse effects, such as psychotic syndromes or jaundice, are more rarely observed. They essentially occur in cases of overdosage in malnourished patients and those presenting previous hepatic or psychiatric conditions. Hepatic toxicity is more frequent in patients over 35 years of age.

2.1.2. Rifampicin (R)

Rifampicin is a potent bactericide that is mainly active on slowly multiplying bacillus populations. It comes in 150 mg, 300 mg, and FDC tablets or capsules.

Dosage and administration

Children < 30 kg: 15 mg/kg/day; maximum 600 mg/day
Children ≥ 30 kg and adults[2]: 10 mg/kg/day; maximum 600 mg/day
Special attention should be given to the risk of overdosage in children and malnourished patients.

Rifampicin should be taken on an empty stomach or at least 30 minutes before meals, since its absorption is reduced by food.

Adverse effects

Rifampicin is generally well tolerated at recommended doses. Severe adverse effects, such as thrombocytopenic purpura, are rare, and more likely to occur under intermittent therapy. Flulike syndrome syndrome may occur with intermittent treatments and recede when the drug is taken daily.

Toxic jaundice is rare, most often spontaneously regressing when treatment is interrupted. After clinical resolution, treatment will be resumed at doses not exceeding 8 mg/kg/day. Biological surveillance of hepatic function is rarely possible. A mild rise in hepatic enzymes and bilirubin is frequent at the beginning of the treatment, but is generally transitory and not predictive of hepatitis.

Overdosage of rifampicin may cause jaundice, above all when associated with isoniazid.

Rifampicin causes an orange-red discolouration of the body secretions (urine, saliva, sweat, tears).

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2 Adult doses should be used for children older than 10-13 years. For simplification the cut-off has been set at 30 kg.

Rifampicin interacts with ARV drugs and fluconazole (pages 67-69).
It reduces the effectiveness of oral contraceptives; higher dosage of oestrogen (50 micrograms) or use of a non-hormonal method is necessary.
Dosages of corticosteroids, cimetidine, digitalics, hypoglycaemics and anticoagulants have to be increased.

Pregnant women

Rifampicin can increase the metabolism of vitamin K, resulting in clotting disorders. Prophylactic administration of vitamin K to mothers and neonates when the mother has received rifampicin during pregnancy is recommended:
– For the mother:
phytomenadione (**vitamin K**) PO: 10 mg/day for the 15 days prior to expected date of delivery. Even with this maternal prevention, the infant still needs to be given prophylactic IM vitamin K treatment to prevent haemorrhagic disease of the newborn.
– For the newborn infant:
phytomenadione IM: 1 mg as a single dose, the day of birth

Note:

Rifabutin has a spectrum of activity similar to that of rifampicin; it is used instead of rifampicin for the treatment of TB among patients taking ART that includes nevirapine or protease inhibitors. It comes in 150 mg capsules.
Rifabutin dosage depends on the ARV used concomitantly (see page 68); dosage adjustment is required in patients with severe liver dysfunction.
Rifabutin is usually well tolerated at recommended doses. Neutropenia, gastrointestinal symptoms, arthralgias, rash, flulike syndrome, and uveitis have been reported.
Hepatotoxicity and range of interactions: similar to rifampicin.

Bleeding disorders in pregnant women and neonates: similar to rifampicin.

Like rifampicin, rifabutin causes an orange-red discolouration of the body secretions (urine, saliva, sweat, tears).
Unlike rifampicin, its absorption is not reduced by food.

2.1.3. Pyrazinamide (Z)

Pyrazinamide is a bactericide that acts against slowly multiplying bacillus populations in acidic inflammatory tissue. The destruction of this bacillus population is important for avoiding the occurrence of relapses and reduces the length of treatment. It comes in 400 mg, 500 mg, and FDC tablets.

Dosage and administration

Children < 30 kg: 35 mg/kg/day; maximum 2 g/day
Children ≥ 30 kg and adults: 25 mg/kg/day; maximum 2 g/day

This drug is used in combination with isoniazid and rifampicin in the intensive phase of short regimens.

Pyrazinamide is contraindicated in patients with severe hepatic impairment.

Adverse effects

Pyrazinamide is usually well tolerated, however arthralgia may occur; it is treated with aspirin and disappears when treatment terminates.

Pyrazinamide is, along with isoniazid, the anti-TB drug most often responsible for hepatic disorders (jaundice).

2.1.4. Ethambutol (E)

Ethambutol is a compound synthetic drug with a principally bacteriostatic action. It comes in 100 mg, 400 mg and FDC tablets.

Dosage and administration

Children: 20 mg/kg/day
Adults: 15 mg/kg/day; maximum 1200 mg/day

Patients should be warned that they must immediately report to a doctor in case of sight deterioration (perception of red and green colours, in particular). The dosage must be carefully calculated according to the weight, especially for children less than 5 years, as it is more difficult to detect sight disorders at this age.

Adverse effects

This drug may cause retrobulbar optic neuritis characterized by visual disturbances: reduction of visual acuteness, blurred vision, central scotoma, and dyschromatopsia. This ocular toxicity depends on dosage and is rarely observed if the dose does not exceed 20 mg/kg/day for 2 to 3 months. Visual alterations are usually reversible a few weeks after stopping ethambutol.

2.1.5. Fixed-dose combinations (FDC)

The fixed-dose combination (FDC) incorporates 2 to 4 different drugs within the same tablet. Their use is of great advantage to improve adherence and to avoid patients taking only part of their prescribed medications. However, be sure of their quality, especially regarding the bioavailability of rifampicin.

Recommended formulations include:

Daily treatment in adults:

4FDC : (**H** 75 mg, **R** 150 mg, **Z** 400 mg, **E** 275 mg)
3FDC : (**H** 75 mg, **R** 150 mg, **Z** 400 mg)
2FDC : (**H** 75 mg, **R** 150 mg)
(**H** 150 mg, **E** 400 mg)

Daily treatment in children:

3FDC : (**H** 30 mg, **R** 60 mg, **Z** 150 mg)
2FDC : (**H** 30 mg, **R** 60 mg)
2FDC : (**H** 60 mg, **R** 60 mg)

Intermittent treatment in adults:

2FDC : (**H** 150 mg, **R** 150 mg)
2FDC : (**H** 60 mg, **R** 60 mg)

Daily doses to be administered (number of tablets/day) are given in Appendix 4.

2.2. Injectable drugs

2.2.1. Streptomycin (S)

Streptomycin is the only first-line drug administered parenterally. It comes in 500 mg and 1 g vials.

Streptomycin is an extremely active bactericide that acts against rapidly multiplying bacillus populations. This explains its advantage during the first weeks of treatment in obtaining rapid negative sputum smear results.

Dosage and administration

Children and adults: 15 mg/kg; maximum 1 g/day in adults.
Reduce the dose to 500-750 mg/day in patients > 60 years or < 50 kg.

Streptomycin is contraindicated in pregnant women (risk of ototoxicity for the foetus).
Women in childbearing age should have a pregnancy test before starting a treatment with streptomycin.

Adverse effects

Hypersensitivity reactions are not uncommon and may be severe (fever, skin reactions), requiring treatment interruption.

Streptomycin has a selective toxic action on the eighth cranial nerve. Vestibular disorders are much more frequent than auditory disorders. Transient dizziness and numbness, particularly around the mouth, are not uncommon after injections. If these symptoms become aggravating, the dose should be reduced. Persistent and severe blackouts, vertigo, ringing in the ears, ataxia, and deafness may be manifestations of chronic toxicity and may become permanent. These symptoms progressively regress, more or less completely so when administration of the drug is stopped.

2.3. Recommended doses

Their dosages have to be adjusted regularly to the patient's weight during the course of treatment.

Anti-TB drugs	**Daily treatment** (in mg/kg)		**TIntermittent treatment three times/week*** (in mg/kg)
	Children	Adults	
Isoniazid (H)	10 (10-15)	5 (4-10)	15
Rifampicin (R)	15 (10-20)	10 (8-20)	15
Pyrazinamide (Z)	35 (30-40)	25 (20-30)	50
Streptomycin (S)	15	15	15
Ethambutol (E)	20 (15-25)	15	30

* Intermittent treatment should be kept for adults in continuation phase and for specific situations (see *Therapeutic regimens*, page 65).

To calculate an anti-TB drug order, see Appendix 5.

3. Management of adverse effects

An anti-TB treatment always involves a combination of at least 2 and up to 5 different drugs. When a reaction occurs, it is important to identify the responsible product, then evaluate the risk compared to adverse effects and interruption or modification of treatment, which would leave an active TB poorly treated.

Adverse effects should be sought during patient follow-up because, even though rarely severe, they can cause patients to interrupt their treatment. Some reactions are specific to a particular drug (e.g. optical neuritis and ethambutol). These reactions and the approach have been described in the section presenting the first-line anti-TB drugs.

Two types of adverse effect are non-specific and may be caused by any anti-TB drug: cutaneous or generalized hypersensitivity and hepatitis.

3.1. Cutaneous or generalized hypersensitivity

The drug most often responsible for these reactions is streptomycin. Hypersensitivity reactions usually appear early during treatment, often in the first four weeks (but rarely during the first week).
One should always eliminate other causes, e.g. scabies.

Hypersensitivity reactions show up in the form of itching and skin rashes. General signs, such as fever, dizziness, vomiting and headache, may occur. Severe —even lethal— exfoliative dermatitis may occur very occasionally (Stevens-Johnson's syndrome), particularly if administration of the drug continues after initial signs of hypersensitivity appear

– Simple itching necessitates symptomatic treatment, e.g. antihistaminic treatment, without interrupting or modifying treatment.

– If a skin rash appears:
  • Stop anti-TB drugs; give symptomatic treatment (no corticoids except in emergencies) and wait for disappearance of symptoms.
  • Test first the drugs least likely to have caused the reaction on the patient (streptomycin being last).
  The aim is to identify the drug that caused the reaction and re-start treatment as rapidly as possible.
  Use the trial doses given in the following table: start with isoniazid over 3 days then add rifampicin over 3 days, etc.

Trial doses for detecting cutaneous or generalized hypersensitivity to anti-TB drugs

Drug	Likelihood	Trial dose		From Day 3
		Day 1	Day 2	
Isoniazid	Least likely	50 mg	Full dose	Full dose
Rifampicin		75 mg	300 mg	Full dose
Pyrazinamide		250 mg	1 g	Full dose
Ethambutol		100 mg	500 mg	Full dose
Streptomycin	Most likely	125 mg	500 mg	Full dose

If the initial reaction to treatment was severe, a weaker trial dose should be used (approximately 1/10th of the dose indicated for Day 1).

Note:
Thioacetazone is a bacteriostatic drug that is no longer recommended as a first-line drug but still used in some countries. It may cause skin reactions, more severe than with other anti-TB drugs, and may result in Stevens-Johnson's syndrome if the administration of the drug is not stopped in time. Most of the severe reactions occur during the first weeks of treatment. They are much more frequent in HIV patients (thioacetazone should not be used if HIV prevalence is high).
In case of simple itching, do not wait for skin rash: **stop treatment immediately**. After complete resolution of symptoms, resume treatment with ethambutol in place of thioacetazone.
Patients presenting even a minor reaction to thioacetazone should never undergo desensitization, nor should they ever receive thioacetazone again.

3.2. Hepatitis

All anti-TB drugs may cause hepatitis. The drugs most often at fault are isoniazid and pyrazinamide. Some combinations, such as isoniazid-rifampicin, potentiate the hepatotoxic effect of each drug.

Clinical aspects resemble that of viral hepatitis: anorexia, nausea, vomiting, jaundice, etc.

When such symptomatology occurs, **all anti-TB drugs should be stopped** while waiting for resolution of signs. Treatment with the same drugs may, most of the time, be resumed without incident. The objective is to resume treatment either with the initial regimen or with another, and as rapidly as possible.

When the clinical status of the patient does not allow interruption of TB treatment, the least toxic drugs, S and E, can be used while waiting for clinical resolution of the hepatitis. In the rare event of recurrent hepatitis or severe hepatic impairment, an alternative treatment might be used: 2 SHE/10 HE.

4. Therapeutic regimens

4.1. Standard treatment regimens

Antituberculous treatments are divided into 2 phases: an intensive phase and a continuation phase.

In order to standardize the treatments, 2 treatment categories are used:

Category 1: treatments for *new* M+, M– and EP cases

Category 2 (re-treatment regimens): treatment for "*non new*" cases, i.e. relapse, failure, return after default and others

4.1.1. Category 1 (6 months)

2 HRZE/4 HR or **2 SHRZ/4 HR**

The regimen 2 HRZE/4 HR is used for treating new M+, M– or EP cases, except those with TB meningitis or miliary TB with meningeal involvement, that require 2 SHRZ/4 HR.

The intensive phase lasts 2 months, with an association of 4 anti-TB drugs (2 HRZE or 2 SHRZ). This phase should be prolonged one month further if sputum smear remains positive after 2 months.

The continuation phase lasts 4 months with 2 anti-TB drugs (H and R).

Note: the 8-month regimen 2 HRZE/6 HE or 2 SHRZ/6 HE is still used by some national programs, however it has been demonstrated that it gives more frequent relapses and failures than the 6-month regimen (12% versus 3%). This regimen should be replaced by the 6-month regimen.

4.1.2. Category 2 (8 months)

2 SHRZE/1 HRZE/5 HRE

This regimen is only used for treating TB patients that are relapse, failure, TAI (treatment after interruption), or others.

The prescription is based on microscopy results and/or the previous treatment history of patients.

The initial phase includes an association of 5 anti-TB drugs (SHRZE) for 2 months, then 4 anti-TB drugs (HRZE) during the third month. The latter phase should be continued for another month with 4 anti-TB drugs if sputum smear remains positive after 3 months.

The continuation phase lasts 5 months with 3 anti-TB drugs (HRE).

Z should be added in continuation phase when E has been used previously in the continuation phase for the Category 1 treatment of the patient: 2 SHRZE/1 HRZE/5 HRZE.

In the event of suspected "failure" after a previous Category 1 treatment, it is recommended, when possible, to perform a DST in order to diagnose possible resistance and adapt the treatment if necessary. The Category 2 regimen is used as a stopgap, when DST is not available.

Notes:
Whether Category 1 or Category 2 regimen:
– It is not recommended to prescribe an intermittent therapy during the intensive phase as some studies have shown that an intermittent therapy is less effective than a daily treatment.
– Intermittent therapy (3 times weekly) can be considered during the continuation phase only, if more convenient for the patient. In this case, supervision is necessary. The negative impact of missing a day of treatment would be greater than in daily treatment.

4.2. Other treatment regimens

2 STH/10 TH (or **2 SHE/10 HE** or **2 SHE/10 TH**)

Except for the potential of this regimen for patients with adverse effect such as hepatitis due to R or Z, this treatment is no longer relevant.

2 SHR/7 HR or **2 HRE/7 HR**

These 9-month regimens may still be useful for patients who cannot tolerate Z.

Manyatta regimen: **2 SHRZ/2 HR(Z)/3 HE** or **2 HRZE/2 HR(Z)/3 HE**

This regimen is used in the Kenyan national programme for treating nomads. Supervision of drug administration is recommended during the first 4 months of treatment, with patients being assembled in TB villages, called "Manyatta" villages.

The *raison d'être* of this regimen, which is meant for populations assumed to be particularly unstable, is that the intensive phase, extended to 4 months, theoretically allows a cure rate of at least 85%, even in patients who default at this point. The administration of H and E for 3 extra months allows a higher rise in cure rates.

5. Treatment of TB in HIV patients

Treatment of TB should be an integrated part of HIV care. Patients should be followed in the same place, by the same health care provider and at the same time for both pathologies.

5.1. Treatment regimens

Treatment of TB in HIV patients follows the usual TB regimens containing rifampicin. Case definitions, treatment categories, sputum examination follow-up, and treatment outcomes are equally applicable for HIV patients.

First-line anti-TB drugs are used in the same dosage and on the same schedule for all patients, regardless of their HIV status. However, some authors recommend a more individualized approach to determine treatment duration: patients who are slow to become sputum smear-negative or continue to have symptoms after the second month of therapy may have their therapy extended to 9 months.

5.2. Concomitant treatments

5.2.1. Interactions rifamycins-antiretrovirals

If HAART (Highly Active AntiRetroviral Therapy) is available for HIV patients, interactions between rifamycins-NNRTIs and rifamycins-PIs must be expected due to liver enzyme induction of the rifamycins.

a) **Treatment of TB in a patient who receives ART**

Non-nucleoside reverse transcriptase inhibitors (NNRTI):
Rifampicin cannot be used with NVP but may combined with EFZ.
Rifabutin can be combined with NVP.
If the patient is receiving NVP when TB is diagnosed:

- If rifabutin is available: give 2 HEZRifabutin/4 HRifabutin.
- If rifabutine is not available, replace NVP with EFZ 600 mg. When the TB treatment is completed, NVP may be resumed.

Nucleoside reverse transcriptase inhibitors (NRTI):
Rifampicin can be safely combined with NRTIs.

Protease inhibitors (PI):
According to current knowledge, when given to the same patient, PI serum levels might be decreased to non-therapeutic levels, while the rifamycins serum levels might rise to toxic levels.
Rifabutin is a less powerful enzyme inducer than rifampicin. It may be used in its place, if available.

	rifampicin	rifabutin
NNRTI		
nevirapine (NVP)	Do not combine	May be combined **rifabutin**: 300 mg/day or 300 mg 3 times a week **NVP** : usual dose
efavirenz (EFZ)	May be combined **rifampicin**: usual dose **EFZ**: 600 mg/day	–
NRTI		
abacavir (ABC)	May be combined without dose adjustments	–
didanosine (ddI)		
lamivudine (3TC)		
stavudine (d4T)		
tenofovir (TFV)		
zidovudine (AZT)		
PI		
indinavir (IDV)	Do not combine	May be combined **rifabutin**: 150 mg/day or 300 mg 3 times a week **IDVr** : 1 g every 8 hours
lopinavir/ritonavir (LPV/r)	Do not combine	May be combined **rifabutin**: 150 mg every other day or 150 mg 3 times a week **LPV/r**: usual dose

b) **Decision to start ART in a newly diagnosed TB co-infected patient:**

CD4 < 200/mm^3	Start TB treatment. Start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months); particularly in patients with severe immunodepression. EFZ containing regimen.
CD4 between 200 and 350/mm^3	Start TB treatment. Start ART after 8 weeks. EFZ containing regimen (or NVP containing regimen in case of rifampicin-free continuation phase).
CD4 > 350/mm^3	Start TB treatment. Start ART if other non-TB stages III or IV events are present. Defer ART if no other non-TB stages III or IV events are present; re-evaluate patient at 8 weeks and at the end of TB treatment (including CD4)
CD4 not available	Start ART treatment as soon as TB treatment is tolerated (between 2 weeks and 2 months).

5.2.2. Interaction fluconazole-rifampicin

These two drugs interact on the blood concentration of each other.

It is recommended that doses be separated by 12 hours (rifampicin in the morning, fluconazole in the evening). In that case, there is no need to adapt rifampicin dosage: blood concentration should be about the same as without fluconazole. However, rifampicin may decrease blood concentration of fluconazole (25-50%): carefully monitor this clinically, and if no improvement is shown, increase dosages of fluconazole.

In oral candidiasis, miconazole gum-patches (prolonged release) should also be used. There is no interaction with rifampicin as miconazole is not absorbed.

5.2.3. Corticoids

Though corticoids are immunosuppressive, they may still be used safely with many HIV patients, depending on the immune status and concurrent infections.

Never start corticoid treatment before anti-TB therapy.

5.2.4. Cotrimoxazole

It is recommended that cotrimoxazole prophylaxis be started or continued during the TB treatment. Studies have shown that cotrimoxazole prophylaxis is associated with a reduced risk of death.

Prophylaxis against other opportunistic infections should continue during TB therapy.

5.3. Approach to adverse effects

Adverse effects are more frequent in HIV patients and may require interrupting the treatment or discontinuing an important TB drug.

5.3.1. Thioacetazone

Thioacetazone is not recommended (increased risk of serious skin reactions).

5.3.2. Isoniazid

HIV patients are more likely to develop isoniazid-related peripheral neuropathy. These patients should receive **pyridoxine** (**vitamin B6**) PO: 10 mg/day of or 25 mg twice a week.

5.3.3. Desensitization

Desensitization is sometimes used for patients who experience adverse effects with essential TB medications that need to be reintroduced.

Desensitization should not be attempted in HIV patients.

5.4. Treatment in children with HIV

The Category 1 regimen 2 HRZE/4 HR is recommended.
If the clinical response is slow, then prolonging the continuation phase by 3 months might be considered (7-month continuation phase).

5.5. Immune Reconstitution Syndrome (IRS)

IRS is a consequence of restoring immune response. It consists in a paradoxical worsening of symptoms observed after the initiation of ART, with recrudescence of TB symptoms (fever, worsened respiratory signs and X-rays, enlarging lymphadenitis, increased pleural fluid).

In most cases these reactions are self limited and rapidly overbalanced by the positive effect of the ART and TB treatment. If needed, administer a corticosteroid (see page 72).

The range of IRS occurrence is between 10 and 180 days, with a median of 2-4 weeks after ART initiation.

5.6. Outcome

TB incidence is reduced by 80% in patients on ART, however it remains higher than in patients that are not infected with HIV.

In absence of ART mortality at one year following the start of TB treatment is 20% greater in HIV patients than that of HIV-negative patients. This excess mortality cannot be entirely attributed to TB, as other serious conditions often supervene. Mortality is less for HIV patients taking the 6-month rifampicin-containing regimen (rifampicin has a broad spectrum of activity and protects against other infections).

Relapse rates are higher in HIV patients.

6. Treatment of DR-TB

6.1. MDR-TB

The individualized treatment of DR-TB usually requires patient's DST to prescribe an association of drugs that are proven or are likely to be effective. The treatment lasts at least 18 to 24 months.
This treatment cannot be self-administrated as it is very poorly tolerated. Direct supervision of treatment is advisable. A daily assessment of adverse effects by the medical team and active patient support are required to improve tolerance and adherence.
Drugs must be taken 6 or 7 days per week.

Regular microbiologic control (sputum, culture, and DST) and control of liver and renal function, as well as electrolytes must be performed.

In all cases, maximal doses will be used as this provides the best chance of cure, with adverse effects treated aggressively and comprehensively. Dose reductions will be reserved for patients with renal impairement or unable to tolerate adverse effects despite appropriate treatment. In general, drugs should not be “held in reserve” for use in case of failure or relapse. The most effective regimen should be given from the start, as the first attempt is likely the only significant chance for cure.

The intensive phase usually includes one injectable agent (capreomycin or kanamycin or amikacin), 3 to 4 drugs among the following: moxifloxacin or levofloxacin, ethionamide, cycloserine or PAS, as well as pyrazinamide and ethambutol if the bacillus is still susceptible. Since fluoroquinolones are bactericide, they should always be used if the bacillus is susceptible.
The injectable drug is administered for at least 6 months (duration of intensive phase). The oral treatment is continued for 15 to 18 months (duration of continuation phase).

6.2. PDR-TB

Treatment regimens for PDR-TB are shorter and better tolerated. They follow specific algorithms according to initial resistance pattern. In places where DR-TB is frequent it is advisable to perform a systematic DST at admission in order to detect and treat PDR-TB before they become MDR-TB.

7. Corticoids in TB

7.1. Indications

- Meningitis with impaired consciousness or neurological defects
- Effusions: pleural with severe respiratory difficulties, or pericardial
- Compressions: laryngitis with obstruction of upper respiratory airways; urinary tract TB (in order to prevent ureteric stenosis); lymph node hypertrophy with bronchial or arterial compression
- Severe hypersensitivity to TB drugs (although effectiveness of corticoids has not been demonstrated)
- Paradoxical reactions (IRS) in the beginning of ART or TB treatment

7.2. Dosage and administration

Dosage and duration of treatment vary according to the severity of symptoms and clinical response.

prednisolone PO:
Children: 2 mg/kg once daily in the morning
Adults: 30 to 60 mg once daily in the morning
If the treatment lasts over 4 weeks, it is recommended to gradually reduce the dose.

8. Indications of hospitalisation

Most cases can be treated as outpatients. If hospitalisation is required, the duration of stay should be as short as possible. Patients should be discharged as soon as their clinical condition allows.

Indications of hospitalisation:

- Severe forms of the disease:
  - haemoptysis, pleural effusion, advanced disease
  - miliary TB, meningitis, Pott's disease, etc.
- Fragile or particular cases:
  - the elderly
  - diabetics, etc.
- Severe adverse effects

There is no specific diet for TB patients. During hospitalisation, food should be given in sufficient quantity (2,800 Kcal/day in average for adults) and adapted to the local feeding habits.
Children who have an actual nutritional problem should be cared for as other malnourished children.

9. Adherence to treatment

Failure to take TB drugs consistently or stopping the treatment too soon can lead to relapse or treatment failure, and contribute to the development of resistance, which may complicate subsequent treatment[1].

In practice, situations requiring administration of the treatment under direct observation by a third party (Directly Observed Therapy or DOT) are limited[2]. Whenever possible, it is preferable that the patient take his medications himself (self-administered treatment or SAT).

A high degree of patient involvement (commitment) is needed to ensure that the patient continues to follow instructions and prescriptions (drug dosages and schedule, length of treatment, diligence in coming in for follow-up visits, etc.) for the entire length of the treatment.

It is crucial that the patient understands the treatment, and that the clinic is organized in such a way that the patient can follow the treatment properly all the way to completion.

9.1. Promoting adherence

There are several factors that can influence adherence. While it is not always possible to control all of these factors —particularly those related to the *patient*— it is possible to at least control the *treatment* and *therapeutic environment*-related factors.

9.1.1. Patient-related factors

How the patient views his illness can be critical. A patient might continue or abandon treatment because he sees, or does not see, improvement. He might have trouble taking an active part in treatment if he attributes his illness to supernatural causes.

Socioeconomic (having a job, a home, family or other support, being stigmatized or marginalized) and psychological factors have an impact on adherence.

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1 Patients who stop their treatment prematurely risk a relapse; the earlier they stop, the higher the risk. If the treatment is interrupted during the intensive phase (and especially if the interruption occurs very early on), they may become sputum smear-positive again within a few weeks (or fail to become smear-negative). If treatment is interrupted immediately after a correctly conducted intensive phase, about 50% of patients will be cured, but 50% will fail to become negative or will relapse within two years. Patients who are inconsistent in following their treatment pose a problem in terms of both treatment failure and the selection of resistant microorganisms.

2 In some cases, treatment is administered under direct observation, but DOT is limiting for patients and hard to implement. Furthermore, it has not been proven to improve results when compared to self-administered treatment. Experience with other chronic diseases has shown that with guidance and support, patients can be independent rather than supervised. In practice, there are a limited number of situations in which DOT is necessary:
- prison: risk of drugs being sold or stolen,
- patient incapable of taking drugs on their own,
- second-line treatment; drugs are toxic, not well-tolerated due to severe adverse effects and thus ill-suited to self-administration.

Personal difficulties should be discussed at patient visits. Solutions, when they exist, will depend on the context and the patient's problem, and need to be found on a case-by-case basis.

9.1.2. Treatment-related factors

– Simplicity of treatment improves adherence. Increasing the number of drugs is detrimental to adherence. The use of FDCs simplifies the treatment by reducing the number of tablets. In addition, it also prevents the selection of drugs by the patient.
– It is essential to quickly detect and manage adverse effects, which are often the reason why patients interrupt their treatment.

9.1.3. Factors related to the therapeutic environment

Practical aspects

– The proximity of drug distribution centres limits the number of patients who default due to transportation problems.
– Patient welcome is important: waiting times at clinics should be reasonable. For hospitalized patients, accommodations (comfort, food, heating, etc.) should be suited to a long-term stay.
– Free care (visits, lab tests and treatment, including adverse effects) limits the number of patients who default for financial reasons.
– Coordination with the HIV clinic, so that TB-HIV co-infected patients can receive treatment for both diseases at the same place and time, spares the patient travel and multiple visits.
– Drug supply management must be rigorous. It is essential to avoid drug shortages, which can lead to treatment interruption and negatively impact adherence (patients waste time in pointless travel, lose confidence in the clinic).
– To anticipate possible problems, give the patient a few extra days' worth of treatment, in case he cannot come get his drugs on the scheduled date.

Patient support and guidance

Therapeutic education
Therapeutic education consists of:
– informing the patient about the disease, the transmission, and the treatment process, its benefits and constraints, the need to follow it faithfully, etc.
– helping the patient incorporate the treatment into his daily life
– answering the patient's questions throughout the entire treatment
See Appendix 6.

Patient support
Listen to the patient, give him encouragement, and gain his trust, so that he does not have to hide the fact that he has forgotten or made a mistake in his treatment. These things happen fairly often, and it is important to know about them in order to help find solutions.
Meet the patient's needs (psychological and/or material help) to whatever extent possible.

Patient support and guidance is the shared responsibility of the entire health care team.
In large-scale projects, the health care team sometimes includes a team of counsellors to provide information and support.
Patient support and guidance is a continuous process, because adherence to treatment varies over time, and any patient can go through phases of treatment acceptance and rejection.

9.2. Measuring adherence

Adherence is regularly measured, indirectly, by:
– standard cohort analysis: cure, default, failure and conversion rates;
– patient's presence at scheduled appointments;
– checking TB treatment cards.

For direct assessment, cross-sectional studies can be conducted on a representative sample of patients:
– objective measures: lab analyses (presence of isoniazid in the urine) or urine colour (rifampicin).
– subjective measures: questionnaire asking the patient to estimate his degree of compliance.

10. Patient follow-up

Patients should be followed for the entire duration of the treatment. Follow-up includes, in particular, assessing the treatment results, adjusting the treatment, if necessary, and detecting and managing adverse effects and adherence problems.

10.1. Category 1 treatment

Schedule of visits and bacteriological examinations during Category 1 treatment

Month	0			1		2		3		4		5	6
Clinical visits	*	*	*	*	*	*		*		*		*	*
Bacteriological testing	*					*				*			*
Adherence	*	*		*		*		*		*		*	

10.1.1. Clinical visits

Frequency will depend on the patient's clinical condition and evolution. On average, for an outpatient who is not having any particular problems, the recommendation is weekly visits during the first month, a visit every other week during the second month, and once a month thereafter.
The patient should be weighed at each visit so the dosages can be adjusted, if necessary.
Visits should coincide with bacteriological testing, when done.

10.1.2. Bacteriological examinations

Patients who start out M+ have their sputum examined 3 times, according to the following schedule:
– for 6-month treatment regimens: at 2 months, at the end of the 4th month, and at the end of treatment (see algorithm page 79);
– for 8-month treatment regimens: at 2 months, at the end of the 5th month, and at the end of treatment.

Examination at the end of the intensive phase

In initially M+ patients
Everyone has a sputum smear performed at 2 months.
If the smear is negative, begin the continuation phase.
If the smear is still positive, prolong the intensive phase for an additional month, then retest. Even if the smear is still positive at this stage, begin the continuation

phase; these are generally patients who started out with high bacillary loads and still have dead bacilli in their sputum. In most of these patients, sputum will later test negative.
A positive smear after 2-3 months of intensive phase treatment should not be considered treatment failure, and does not justify switching to Category 2 treatment.

In initially M– or EP patients
Not everyone is tested. Smears are performed only if an M– PTB patient fails to improve, or if an EPTB patient develops pulmonary signs. A positive smear at the end of the intensive phase is considered a treatment failure, and justifies switching to Category 2 treatment. Attempt to confirm the failure via culture (and DST).

Month 4 examination

In initially M+ patients
If the smear is negative, pursue the continuation phase to completion.
A positive smear at this point meets the standard definition of treatment failure.
Patients in treatment failure start Category 2 treatment (re-treatment).
Be careful when defining failure on the basis of microscopy alone; a positive smear might be due to the presence of dead bacilli, especially in patients who started out with a high bacillary load.
Attempt to confirm the failure via culture (and DST).
– If the culture is negative and clinical evolution is good: this is not a treatment failure. The patient, who was receiving Category 2 treatment while awaiting the culture results, goes back to the Category 1 treatment.
– If the culture is negative and clinical evolution is poor: continue Category 2 treatment and culture again.
– If the culture is positive and the patient is clinically stable: continue the Category 2 treatment, adjusting it later, if necessary, according to DST results.

Patients with a positive culture and worsening clinical condition are considered MDR-TB suspects. MDR-TB requires special management, which is not covered in this guide.

In initially M– or EP patients
Not everyone is tested. Smears are done only if an M– PTB patient fails to improve, or if an EPTB patient develops pulmonary signs. A positive smear 4 months after starting treatment corresponds to treatment failure, and justifies switching to Category 2 treatment. Attempt to confirm the failure via culture (and DST).

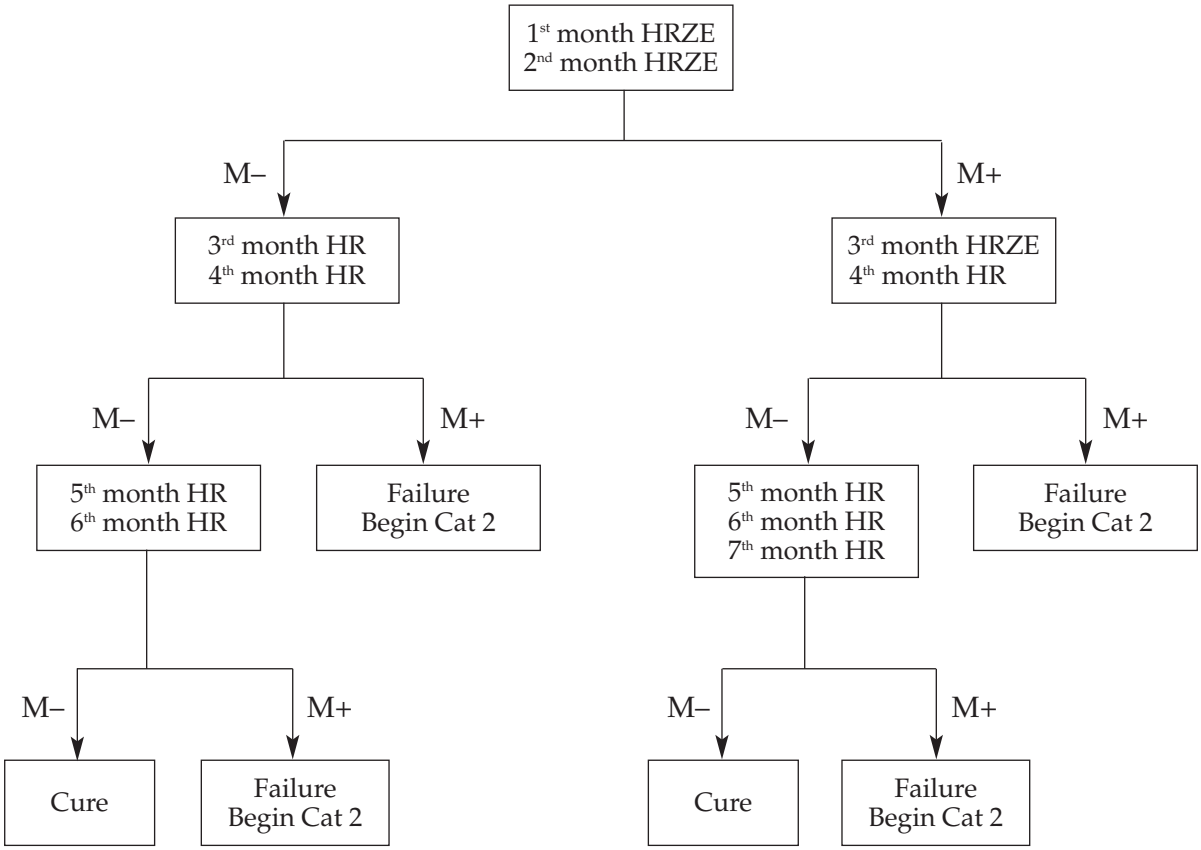
End of treatment examination

Following this test, the treatment outcome is established (“cure”, “treatment completed”, etc.).

In initially M+ patients
A negative smear at the end of treatment corresponds to a cure.
While it is unlikely that sputum would be positive again at this stage, this would justify switching to Category 2 treatment. An attempt would have to be made to confirm the failure via culture (and DST).

In initially M– or EP patients
A first positive smear at this stage is extremely unlikely.

Bacteriological follow-up
Category 1 (2 HRZE/4 HR)



10.1.3. Patient information and adherence interviews

The clinician who diagnoses the patient and prescribes treatment should inform the patient about his disease and its treatment. Nevertheless, this initial interview alone is not sufficient to ensure that all the information has been given and taken in.

Interviews are recommended:
- at the start of treatment: 2 interviews devoted to informing the patient (one for informing him, the second for making sure the information has been absorbed);
- at the end of the intensive phase: an interview to explain the treatment changes that accompany the change in treatment phase;
- throughout the treatment: a monthly interview to help assess and encourage adherence.

See Appendix 6.

When there are a large number of patients, interviews devoted to treatment adherence with specially trained personnel may be justified.

10.2. Category 2 treatment

Schedule for visits and bacteriological examinations during Category 2 treatment

Month	0			1		2	3	4	5	6	7	8
Clinical visits	*	*	*	*	*	*	*	*	*	*	*	*
Bacteriological testing	*						*		*			*
Adherence	*	*		*		*	*	*	*	*	*	

10.2.1. Clinical visits

Same as Category 1.

10.2.2. Bacteriological examinations

Patients who start out M+ have their sputum examined 3 times: at 3 months, at the end of the 5th month, and sometime during the 8th month (see algorithm page 82).

Examination at the end of the intensive phase

In initially M+ patients
Everyone has a sputum smear performed at 3 months.
If the smear is negative, begin the continuation phase.
If the smear is still positive, prolong the intensive phase for an additional month, then retest. Even if the smear is still positive at this point, begin the continuation phase; these might be patients who started out with high bacillary loads and still have dead bacilli in their sputum. In some of these patients, sputum will turn negative later.
A positive smear after 3-4 months of intensive phase treatment should not be considered treatment failure.

In initially M– or EP patients
Not everyone is tested. Smears are done only if an M– PTB patient fails to improve, or if an EPTB patient develops pulmonary signs. A positive smear at the end of the intensive phase is considered a treatment failure. Category 2 treatment must be continued. Attempt to confirm the failure via culture, and perform DST for potential adjustment of the treatment.

Month 5 examination

In initially M+ patients
If the smear is negative, pursue the continuation phase to completion.

A positive smear at this point meets the definition of treatment failure. Be careful when defining failure on the basis of microscopy alone; a positive smear might be due to the presence of dead bacilli, especially in patients who started out with a high bacillary load.

Attempt to confirm the failure via culture (and DST):
– If the culture is negative and clinical evolution is good: this is not a treatment failure. Treatment should be continued to completion.
– If the culture is negative and clinical evolution is poor: continue the treatment and culture again.
– If the culture is positive and the patient is clinically stable: continue the treatment, adjusting it later, if necessary, according to DST results.

Patients with a positive culture and worsening clinical condition are considered MDR-TB suspects. MDR-TB requires special management, which is not covered in this guide.

In initially M– or EP patients
Not everyone is tested. Smears are done only if an M– PTB patient fails to improve, or if an EPTB patient develops pulmonary signs. A positive smear 5 months after starting treatment qualifies as treatment failure. Treatment must be continued. Attempt to confirm the failure via culture, and perform DST for potential adjustment of the treatment.

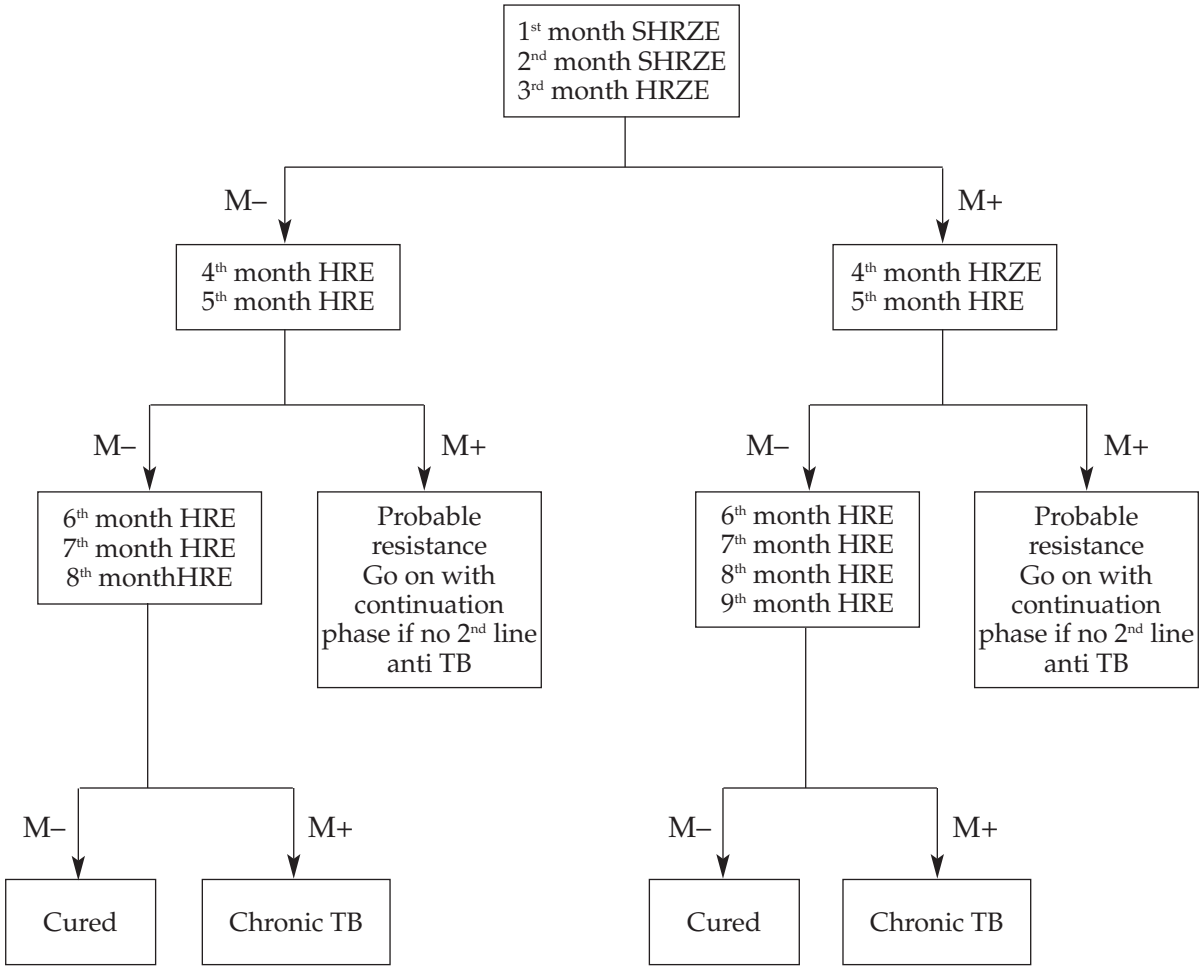
End of treatment examination

Following this test, the treatment outcome is established ("cure", "treatment completed", etc.).

In initially M+ patients
A negative smear at the end of treatment in a patient whose 4-5 month smear was negative corresponds to a cure.
A positive smear at this stage corresponds to treatment failure. Attempt to confirm the failure via culture, and do antibiotic sensitivity testing for potential adjustment of the treatment.

In initially M– or EP patients
A first positive smear at this stage is extremely unlikely.

Bacteriological follow-up
Category 2 (2 SHRZE/1 HRZE/5 HRE)



10.2.3. Patient information and adherence interviews

Same as Category 1.

11. Management of treatment interruption

The approach depends on initial bacteriological status, the moment when the patient returns, and the length of previous treatment.
The question of whether or not a patient still presents an active form of the disease should always be asked. It is possible that, in spite treatment interruption, s/he may be cured (this sometimes happens without treatment) and that a re-treatment may not be justified. In case of doubt, the patient should be monitored and re-evaluated, on a regular basis if possible, before a definitive decision is made.
The approach is, in theory, standardised. However, it is often complex and should be based on rigorous study of the patient's history, an interview, and a meticulous clinical examination, and then completed by bacteriological examination results. An X-ray might be useful if available, and more so if previous ones are available for comparison.
It has been proven that a patient who interrupts may interrupt again more easily than one who has not. The patient should therefore be monitored even more closely and re-motivated with the greatest attention (all the more so as a re-treatment regimen is often the last possible chance of cure).

11.1. Patients initially in Category 1

Length of treatment	Length of interruption	Sputum result at return	Treatment outcome	Classification at return	Treatment action
< 1 month	< 2 weeks	Not needed	–	–	Continue Cat. 1 at the point it was stopped
	2-7 weeks	Not needed	–	–	Re-start Cat. 1
	≥ 8 weeks	M+ M–	Defaulter Defaulter	New New	Re-start Cat. 1 and give the patient a new number
1-2 months	< 2 weeks	Not needed	–	–	Continue Cat. 1 at the point it was stopped
	2-7 weeks	M+ M–	– –	– –	- Re-start Cat. 1 - Continue Cat. 1 at the point it was stopped
	≥ 8 weeks	M+ M–	Defaulter Defaulter	RAD* RAD*	Start Cat. 2 and give a new number to the patient
≥ 2 months	< 2 weeks	Not needed	–	–	Continue Cat. 1 at the point it was stopped
	2-7 weeks	M+ M–	Cancel previous registration –	Others –	- Start Cat. 2 register as "Others" - Continue Cat. 1 at the point it was stopped
	≥ 8 weeks	M+ M–	Defaulter Defaulter	RAD* RAD*	Start Cat. 2 and give the patient a new number **

* RAD = return after default (or TAI = Treatment after interruption)
** For patients having received adequate treatment for 4 months or more before interruption who return smear negative and in good clinical condition the decision to start a Cat. 2 treatment will be considered on a case by case basis.

11.2. Patients initially in Category 2

Length of treatment	Length of interruption	Sputum result at return	Treatment outcome	Classification at return	Treatment action
< 1 month	< 2 weeks	Not needed	–	–	Continue Cat. 2 at the point it was stopped
	2-7 weeks	Not needed	–	–	Re-start Cat. 2
	≥ 8 weeks	M+ M–	Defaulter Defaulter	Same as previous registration	Re-start Cat. 2 and give the patient a new number
1-2 months	< 2 weeks	Not needed	–	–	Continue Cat. 2 at the point it was stopped
	2-7 weeks	M+ M–	– –	– –	- Re-start Cat. 2 - Continue Cat. 2 at the point it was stopped
	≥ 8 weeks	M+ M–	Defaulter Defaulter	RAD* RAD*	Re-start Cat. 2 and give a new number to the patient
≥ 2 months	< 2 weeks	Not needed	–	–	Continue Cat. 2 at the point it was stopped
	2-7 weeks	M+ M–	– –	– –	- Re-start Cat. 2 - Continue Cat. 2 at the point it was stopped
	≥ 8 weeks	M+ M–	Defaulter Defaulter	RAD* Others	Re-start Cat. 2 and give the patient a new number

* RAD = return after default (or TAI = treatment after interruption)

CHAPTER 3

Prevention

1. Infection control in health facilities

TB infection control relies, in general and above all, on early diagnosis and treatment of contagious patients—that is, patients with respiratory (pulmonary, bronchial and laryngeal) TB. With effective therapy, contagiousness declines very rapidly, and may be considered nil after 2 to 3 weeks of treatment.

In health facilities, other measures are needed to reduce the risk of transmission, because the close proximity of contagious TB patients, on one hand, and health staff and vulnerable (particularly immunocompromised) patients, on the other, creates favorable conditions for hospital-acquired TB.

1.1. Prevention plan

Protective measures should be detailed in a written plan that is regularly updated and distributed to staff. This plan should include the different types of protective measures—personal, administrative and environmental. One person should be clearly designated as responsible for implementation and follow-up of the prevention plan.

1.2. Personal protective measures

1.2.1. Health staff

Anti-inhalation masks (Appendix 7)

M. tuberculosis is transmitted mainly via the respiratory route. Only anti-inhalation masks (high-filtration masks) are capable of preventing inhalation of the bacillus.
All members of the staff must wear these masks, whether caregiver or not:
– when in contact with contagious patients,
– when collecting sputum samples and preparing slides and when collecting and disposing of sputum containers.

In addition to wearing a mask—which is a specific protective measure—standard precautions (hand hygiene, gown, etc.) apply in TB wards, just as they do in any other hospital department.

Medical follow-up

Initial check-up:
- Determine the person's immunization status
- Perform a baseline chest X-ray
- Perform a baseline tuberculin test
- Inform the staff that pregnant women and anyone with an immune deficiency (diabetics, HIV+, etc.) should not work in a TB ward. Personnel who come in contact with TB patients must be informed of the links between HIV and TB.

BCG vaccination:
If there are no contraindications, BCG vaccination is recommended for all non-vaccinated personnel with a negative tuberculin skin test, particularly if that person is exposed to DR-TB.
The disadvantage of BCG vaccination is that it makes tuberculin skin test monitoring, and thus diagnosis of primary infection, difficult.

Follow-up:
- A clinical examination should be performed once per year.
- Chest X-rays should not be performed systematically but only in cases where clinical signs are observed.
- Tuberculin skin test: in countries where BCG vaccination is not routine, regular monitoring with a tuberculin skin test (every year or every two years) allows detection of new TB infection. Conversion to a positive tuberculin test justifies prophylactic treatment, after active TB has been ruled out.
  In other countries (the vast majority), the tuberculin skin test is only a diagnostic pointer of active TB, to be interpreted in association with clinical and radiological signs.
  Only an increase of ≥ 10 mm in the diameter of the induration over a previous skin test is considered significant.

1.2.2. Patients and attendants

Masks (Appendix 7)

Contagious patients must wear a surgical mask (anti-projection mask) when they leave their rooms to go to another department or any other enclosed area (except the outdoors). The mask is intended to prevent projection of *M. tuberculosis* by the carrier.

Attendants and visitors must wear a high-filtration mask (like that worn by staff) when entering a contagious TB patient's room.

Informing patients, visitors and attendants

Inform patients, visitors, and attendants about the risk of TB transmission and how to avoid it, or protect themselves: ask patients to cover their nose and mouth when they cough or sneeze, and to use a sputum container; explain why, when and how to use masks; display posters of protective measures in wards, waiting rooms, etc.

1.3. Administrative measures

1.3.1. Identification of high-risk areas (listed from highest to lowest level of risk)

– DR-TB M+ department – M+ re-treatment department

– Sputum collection areas – Sputum smear preparation area (laboratory)

– Diagnosis department – M+ ward

– EP and M– ward – Children's ward – Smear reading (laboratory)

– Kitchen area (non-TB zone) – Administration (non-TB zone)

It is recommended to draw a floor plan of the facility with the different areas.

1.3.2. Patient triage

A member of the medical staff should identify patients with a cough as soon as possible after their arrival at the health facility. Patients with a cough of over two weeks duration should be sent to a separate waiting room. Patients should be tested for TB during the consultation.

1.3.3. Isolation of patients

TB wards must be separated from the others wards in the health structure compound. Within the TB department, patients are placed in different sections according to their resistance risk and degree of contagiousness:
– Highly contagious patients with proven or suspected DR-TB; chronic cases; re-treatment cases
– Contagious patients with fully sensitive disease
– Patients who are undergoing diagnosis as suspected cases
– Patients with smear-negative TB
– Patients with EP forms
– Patients having converted their sputum/culture
– Children

In a context of high prevalence of resistances, it is recommended to have single rooms, in priority for:
– DR-TB (culture positive)

– Suspect cases
– M+ patients waiting for their DST with priority to re-treatment and DR contacts

Separate proven or suspected DR-TB patients from all others TB patients.

1.3.4. Patient, visitor and attendants' movement

Inside the TB department, circulation of patients and attendants is controlled:
– Limit the visits, limit duration of visit, particularly for contagious patients.
– Encourage visits outside the building, in the open air, especially for contagious patients.
– Before any visit, the nurse should provide information on the transmission risk.

1.4. Environmental measures

1.4.1. Ventilation

Natural ventilation is the most effective means for reducing the concentration of *M. tuberculosis* suspended in the air and, as a result, the risk of transmission.

Ventilation should be done with the windows open and inside doors closed, so that the flow of air is directed outside and not toward the corridors. Open the windows several times a day (as much as weather conditions permit).
Create shady spaces so that patients, attendants and visitors can stay outside during the day.

In some cases, natural ventilation is not sufficient; fans should be used. The principle is the same as with natural ventilation: direct room air towards the exterior.

1.4.2. Natural sunlight exposure

The UV-C radiation in natural light inactivates the TB bacillus.
Expose patient rooms and high risk areas to as much natural light as possible, keeping the windows open to let the rays in.
Take bedding and personal belongings out into the sunlight daily, if possible.

1.4.3. Ultra-violet germicidal irradiation (UVGI)

Mycobacterium tuberculosis is sensitive to germicidal radiation of UV found in the UV-C portion of the ultra-violet spectrum.
The use of UVGI lamps is reserved for high-risk areas (laboratory, sputum collection area, poorly-ventilated spaces, etc.), where other environmental measures are not sufficient due to climatic or structural constraints.

Constraints on the use of UV lamps:
– Monthly checking and daily maintenance (dusting).
– Risk of mercury poisoning in case of broken or mishandled lamp; disposal of mercury from used lamps requires specific procedures.
– May not work in humid areas.
– Need to be replaced every 5000 hours (as they begin to emit harmful wavelengths of light. A lamp working 8 hours / day must be replaced every 6 months).
– Use only lamp-type UVC-254 µm, made from mercury and quartz.
– Use only indirect lamps (portable lamps, or those mounted high up and directed toward the ceiling), to avoid possible burns to the conjunctiva or skin from direct exposure. Ensure that the airflow crosses in front of the lamp. Use direct UV lamps in empty rooms only (they can be switched on at night).

1.4.4. Areas necessitating specific measures

Sputum collection area

This area must be settled outside in open air where bacilli will naturally be dispersed by wind and killed by sun rather than in a closed room where the concentration of bacilli will be high.
In cold regions, assign a specific room of small size (1 m^2) with one single glass door opening outside. Keep the door largely open for 5 minutes between each patient. The small volume of air in this room facilitates rapid ventilation.

Laboratory

Laboratory must be provided with easy to clean working surfaces (avoid wood) to allow proper disinfection and large windows (well positioned to the sun) to allow good ventilation and sunlight.
Water-filters should be used to avoid contamination by saprophyte mycobacterium sometimes present in the water.
Sputum smear microscopy must be performed in two separate rooms: one for smearing and staining slides and one for reading.
The use of Biological Safety Cabinet (BSC) is not mandatory for laboratories performing simple smear microscopy except in context of high prevalence of resistances (see Appendix 2.10).

1.5. Hospital hygiene

1.5.1. Hygiene and disinfection

Reusable medical items that come in contact with TB patients (dressing trays, forceps, etc.) should receive the standard treatment: pre-disinfection, cleaning, and sterilization.

Special disinfection of TB patient living quarters is not necessary, provided they are well-ventilated. Ordinary cleaning of rooms and objects (linens, dishes, etc.) used by TB patients is sufficient.
After the patient is discharged, air the empty room well for 2 hours.

1.5.2. Waste management

Sputum containers

– In the wards, sputum containers should be about 200 ml, sealable (if possible), non-sterile containers. Replace the containers daily.
– In the laboratory, sputum containers are smaller (25-35 ml), with hermetic cap, non-sterile and for single use.

Used containers should be collected in a trash bag and incinerated. Do not re-use. Do not fill the containers with chlorine solution before incineration (toxic gases).

Sharps waste and soft waste

Standard infectious healthcare waste treatment.

1.6. Training for the staff

All healthcare personnel should receive initial training on protective measures. Continuing education should be offered regularly—annually, for example.

2. Chemoprophylaxis

Chemoprophylaxis is in fact most often the treatment for primary infection in order to sterilize lesions and prevent the development of active TB. It is more a treatment than chemoprophylaxis, in the literal sense of the term.
It consists in daily administration of isoniazid for 6 months, at a dose of 10 mg/kg/day in children less than 30 kg and 5 mg/kg/day in children ≥ 30 kg and adults.

2.1. Benefit and limitations

Prophylaxis is effective when properly done. It may reduce the risk of developing TB by up to 90% in a patient with primary infection.

However:
- It is often difficult to rule out active TB with certainty, however, it is essential to do so: administering prophylaxis to a patient with active TB would be equivalent of giving him a monotherapy with isoniazid.
- Most studies reveal poor adherence (28-60%), since asymptomatic patients do not see the point of what they consider a long, restrictive treatment.
- The effectiveness of isoniazid prophylaxis depends on the sensitivity to isoniazid. It may be limited in areas where primary resistance to this antibiotic is high.
- The risk of inducing hepatitis with isoniazid alone is not insignificant. It is low in young subjects and progressively increases with age, attaining over 2% in subjects over 50.
- The use of isoniazid is contraindicated in patients with severe or chronic active hepatitis, and it should be administered with caution to patients who regularly consume alcohol.

2.2. Chemoprophylaxis in children

2.2.1. Newborn infants of M+ mothers

In all cases where the mother is still M+ at birth, chemoprophylaxis is administered to the child for 6 months; BCG vaccination is done just afterwards (BCG vaccine should not be given during administration of isoniazid).

- If a child immediately or subsequently presents signs of TB (in general, only evident after approximately 2 to 8 weeks: arrested growth, spleno-hepatomegalia, jaundice, sometimes pneumonia), s/he should undergo complete anti-TB treatment after exclusion of other possible medical causes. This case scenario is unlikely if prophylaxis is correctly administered, but not impossible in cases of primary resistance to isoniazid.

– If a tuberculin skin test is possible, the approach is:
  • To administer isoniazid for 3 months, then do a tuberculin skin test.
  • If the tuberculin skin test is positive, continue isoniazid for 3 more months.
  • If the tuberculin skin test is negative, stop isoniazid and administer the BCG vaccine.

Notes:
– The child should not be separated from her/his mother unless s/he is severely ill. Breastfeeding should continue.
– It is possible that isoniazid is not effective if primary resistance against this drug exists (varies according to the area) or if there is a problem of secondary resistance in the mother. The child must therefore be closely monitored in all cases.
– If a mother presents M– TB during pregnancy or if became negative under treatment, it is sufficient to vaccinate the child at birth and to monitor him/her thereafter.

2.2.2. Children under five years of age in contact with M+ patients

If suspicion of TB exists

Before administering chemoprophylaxis it is imperative to rule out active TB. Clinical and paraclinical examinations (see paediatric scores, page 50) are used to make the diagnosis. If TB is suspected, the child should undergo complete curative treatment. If not, prophylaxis should be administered for 6 months.

If the child is healthy

Administer chemoprophylaxis for 6 months, regardless of the vaccination status of the child. If it is not possible to administer the prophylaxis, vaccinate and monitor the child. The use of a tuberculin skin test may help to better specify indications for prophylaxis. This test is, however, rarely available and is quite often difficult to interpret. In practice, it is simpler and more prudent to systematically administer prophylaxis when indicated.

Daily dose of isoniazid in newborns and children

Weight in kg	**< 3.5**	**3.5 - 5**	**6 - 9**	**10 - 15**	**16 - 20**
100 mg tablet	–	1/2 tab	1 tab	1 1/2 tab	2 tab
50 mg/5 ml syrup	3 ml	5 ml	9 ml	–	–

2.3. Chemoprophylaxis in HIV patients

The use of ART in HIV patients is the best TB prophylaxis, with up to 80% of risk reduction, without having to use isoniazid.

2.3.1. Primary prophylaxis

Isoniazid is used for prophylaxis after TB exposure in those with known HIV infection. Meta-analysis has shown that prophylaxis confers a 40% reduction in TB risk overall. Another study showed that isoniazid preventive therapy provided a mean duration of protection of 2.5 years, though it did not lower HIV-related mortality.

The WHO recommends prophylaxis in asymptomatic HIV patients, i.e. patients who have no cough, no lymph nodes, no fever and no weight loss. Nevertheless, recent studies show that the frequency of active, even asymptomatic, TB is significant in HIV patients.

2.3.2. Secondary prophylaxis

Secondary prophylaxis is administered to HIV patients who have completed curative TB treatment. Some authors recommend that isoniazid be given indefinitely thereafter to prevent recurrence. There is still no consensus on secondary isoniazid prophylaxis.

In practice:
Routine primary or secondary isoniazid prophylaxis in HIV patients is only implemented in the context of studies or pilot projects. The priority remains early detection and treatment of active TB.

2.4. Chemoprophylaxis and DR-TB

When the risk is estimated to be high, some authors recommend 6EZ or an association of ethambutol + fluoroquinolone as chemoprophylaxis. These regimens are poorly tolerated and have frequent adverse effects, leading to poor compliance, and their duration and effectiveness have not been clearly established.
They are not recommended for immunocompetent patients, for whom a regular clinical follow-up is preferred.
Their only indication is for patients with an immunodeficiency, in particular AIDS or HIV infection.
This question is theoretical in most circumstances, as the primary infection remains generally unnoticed.

3. BCG vaccine

3.1. Efficacy

Published studies offer conflicting results, with protection varying from 0 to 80%. Surveys showing high BCG effectiveness appear less controversial than those showing low or no effectiveness. When BCG is correctly carried out, it confers protection that is not insignificant (probably over 50%). It has been proven that BCG protects against severe forms of the disease, in particular TB meningitis and miliary TB.
BCG vaccination does not diminish transmission of TB.

3.2. Vaccination strategy

The question of whether to vaccinate with BCG or not is debated only in developed countries, where risk of infection is low. In countries where TB is highly endemic, the value of vaccination is not questioned.

The WHO recommends vaccination of all newborn infants as soon as possible after birth in order to:
– Allow the maximum number of children to be reached, because in many areas birth is one of the rare occasions when people are in contact with healthcare structures.
– Avoid leaving newborn infants (which may have close contact with potentially contagious adults) without protection for several months.

Children who could not be vaccinated at birth receive BCG in their first year, at the same time as other vaccinations. During vaccination campaigns or at vaccination centres, all children under 15 years of age who do not present a vaccinal scar on their left arm should be vaccinated.
There is no problem in giving a BCG vaccination at the same time as DTP + polio. It is not feasible to conduct a preliminary tuberculin skin test for determining if a child already has a primary infection. There is no contraindication for vaccinating a patient with primary infection or a carrier of active TB.

The objective of a programme is to obtain vaccination coverage of at least 80% in the 0-2 years old age group. This coverage is evaluated during sampling surveys of target populations, based on the presence of vaccinal scars.

It is recommended to vaccinate healthcare personnel (with negative tuberculin skin test), particularly in situations with a significant prevalence of MDR-TB among patients.

Also see *BCG vaccine*, Appendix 8.

CHAPTER 4

Evaluation

1. Definitions of treatment results

The following definitions were drawn up in order to standardize the evaluation of results; they might differ slightly from country to country.

Cured

Patient initially M+, who completed treatment AND has at least 2 negative smears: one at the end of treatment and the other at least one month apart AND for whom there is no culture result
or
Patient initially M+, who completed treatment AND has at least 2 negative cultures: one at the end of treatment and the other at least one month apart, regardless of smear status at the end of treatment
or
Patient initially M+, who completed treatment AND has one negative culture and one negative smear at the end of treatment

Treatment completed

Patient initially M+, who completed treatment but for whom there is no bacteriological verification at the end of treatment
or
Patient initially M+, who completed treatment AND has a positive smear and a negative culture during the last month of treatment
or
Patient initially M– or EP, who completed treatment AND presents significant clinical improvement and gain of weight

Failure

Any patient who has a positive smear at 4-5 months of treatment or thereafter, in the absence of a culture
or
Any patient who has a positive culture at 4-5 months of treatment or thereafter, regardless of smear status
or
Patient initially M– or EP, with no significant clinical improvement and no significant gain of weight after 4-5 months of treatment and for whom the diagnosis of failure is established by a clinician
or
Patient initially M– or EP, who has a positive smear at the end of intensive phase

Death

Patient who died during treatment, whatever the cause of death

Treatment interrupted (default)

Patient who interrupted treatment for over 2 months

Transfer out

Patient transferred to another treatment centre

Treatment adapted

Patient initially treated with a standard regimen Cat. 1 or 2 and for whom the treatment is secondarily adapted according to the results of DST (and not because of a treatment failure).

Note: patients who refuse treatment are registered as "**default before treatment**".

2. Quarterly report

The key evaluation tool is the quarterly report (see Appendix 9.1). It must be presented in a standard manner in two parts: one on case finding, one on treatment results. The data presented in the report come from the TB register (see Appendix 10.3).

2.1. Case finding results

2.1.1. New cases and re-treatments

Cases detected within the previous quarter are counted using the TB register. These cases are then classified according to:
– The form of the disease: PTB M+ or M–, EPTB
– The treatment history (new cases or re-treatments). Re-treatments are registered as relapses, failures, treatment after interruption, others (see *Case definitions*, Chapter 1)
– Gender and age group
– Site of the disease for EP TB

2.1.2. Proportion of M– forms

$$\frac{\text{Number of cases M– x 100}}{\text{Total number of cases}}$$

This indicator essentially depends on:
– Diagnostic means
– The number of children under treatment (children are rarely M+)
– The prevalence of HIV infection within the population (these patients present more M– pulmonary forms)

The proportion of M– is about 20% when HIV prevalence is low, and 30% when HIV prevalence is high. Proportions that differ significantly from these should make one wonder about possible under- or over-diagnosis of M– forms.

2.1.3. Proportion of M+ forms

$$\frac{\text{Number of cases M+ x 100}}{\text{Total number of cases}}$$

In practice, the proportion of M+ should correspond to roughly half of all patients. This proportion is lower, however, in areas where HIV prevalence is high. Proportion of M+ is around 60% where HIV prevalence is low and 40% where HIV prevalence is high.
Proportions that differ significantly from these should make one wonder about possible under- or over-diagnosis of M– and EP forms.

2.1.4. Proportion of new cases

$$\frac{\text{Number of new cases} \times 100}{\text{Total number of cases}}$$

Often low (below 50%) at the early stage of a project as many patients received previous treatment, it should progressively increase and exceed 80% in situations where resistance is not a significant problem. This indicator indirectly reflects the relapse and failure rates and the possible parallel treatments outside the program.

2.1.5. Proportion of children

$$\frac{\text{Number of patients less than 15 years} \times 100}{\text{Total number of cases}}$$

Children should represent approximately 10 to 15% of the total number of patients. Proportions that differ significantly from these should make one wonder about possible under- or over-diagnosis of TB in children.

2.1.6. Case detection rate

A rough estimate of the expected number of new M+ cases can be obtained using the ARI (see *Chapter 1*, page 19 and Appendix 2), which allows an estimate of detection efficacy:

$$\frac{\text{Number of new cases M+} \times 100}{\text{Number of expected cases}}$$

It should be noted that even the best programmes often do not detect more than 60 to 70% of total new M+ cases within a population.

In addition:
– ARI is a rough estimate;
– Patients might come from outside the target area;
– Impact of HIV on TB incidence is difficult to estimate.

2.2. Treatment results

A TB project should be evaluated based on its ability to cure patients, and not just on its ability to find cases and start them on treatment. Evaluation of treatment results is a fundamental stage in the evaluation.

2.2.1. Quarterly cohort analysis

Quarterly cohort analysis is an epidemiological method that provides a rigorous, ongoing assessment of activities.

Principles

A "cohort" is a group of individuals presenting certain common characteristics and undergoing the same events. The follow-up of individuals belonging to a cohort allows the determination of how each individual reacts to these events. In the case of treatment evaluation of TB patients, a cohort is represented by patients all put under treatment within a period of 3 months (one quarter); the event that these patients undergo is the treatment. At the end of treatment, the status of each individual is defined: cured, deceased, defaulted, etc. It is possible to calculate cure rates, default rates, etc. within this group because they are individuals belonging to the same group.

Evaluation dates

Cohort analysis could be carried out when all patients admitted in a given period of time had a chance to complete their treatment. In practice, for simplification, cohort results are analysed quarterly, 1 year after inclusion of the last patient of the cohort, e.g. cohort of patients admitted during the first quarter 2007 will be evaluated at the end of the first quarter 2008.

Results

Treatment results of all forms of TB should be evaluated.
– M+ forms (new cases, re-treatment: relapses, failures and TAI),
– M– and EP forms (new cases and re-treatment) are to be evaluated on the same principles.

Notes:
– If several therapeutic regimens are used in the same project, results can be analysed separately (possibly separated by type of regimen).
– The number of patients in each category should, in principle, be identical to those registered for the same quarter in the *case finding* part of the corresponding quarterly report: if it is different, an explanation should be given.
– Patients in the "transfer in" category should not be included. Their results should be transmitted to the transferring structure (district, camp, etc.) that made the initial decision to treat the patient.

2.2.2. Analysis and interpretation of results

The most important indicators are:

Cure rate

$$\frac{\text{Number of new M+ cases "cured"}}{\text{Total number of new M+ cases put under treatment}} \times 100$$

The rate may also be calculated for M+ patients under re-treatment regimens and in general for all M+ patients under treatment.
This rate is the best indicator of the success of a project for M+ patients.

Default rate

$$\frac{\text{Number of patients registered as "defaulters"}}{\text{Total number of patients put under treatment}} \times 100$$

Patients who default are at risk for not being cured or of relapsing. The higher the default rate, the greater the risk of drug resistance.

Proportion of patients completing treatment

A high proportion of patients completing treatment is a positive sign for patients M– and EP, but for M+ it indicates insufficient bacteriological verification at the end of treatment, a step that should therefore be intensified.

Success rate

Proportion of patients either cured or having completed their treatment. Best indicator to measure the efficacy of a project for all forms of the disease (M+, M–, EP).

Case fatality ratio (CFR)

This ratio should not exceed 5% of treated cases. Over-mortality may be related to the poor functioning of a treatment programme; it may also be due to a high prevalence of HIV infection among cases or late referrals.

Failure rate

All therapeutic regimens have a theoretical optimum effectiveness of over 90% for new M+ cases.
A high failure rate in new cases can be related to poor treatment adherence, high rate of primary resistance, or poor quality of the TB medicines.
The failure rate should not be over 2% in new cases under treatment.

Conversion rate

This rate represents the proportion of new M+ patients who became sputum smear negative after 2 months of treatment, as compared to the number of new M+ patients for whom sputum microscopy was performed. For new cases it should theoretically be over 80%.
Patients who remain positive at 2 months are only considered "failure" if they are still positive at 4 months.
At the beginning of a project, when it is not yet possible to do cohort analysis, the conversion rate is an indicator of the effectiveness of treatment, and allows early detection of potential problems.

Proportion of patients for whom HIV status is known

$$\frac{\text{Number of patients for whom HIV status is known at the end of treatment}}{\text{Total number of patients put under treatment}} \times 100$$

This proportion is one of the indicator that helps evaluate the integration of TB and HIV services.

TB-HIV co-infection rate

$$\frac{\text{Number of HIV+ patients}}{\text{Total number of patients for whom HIV status is known at the end of treatment}} \times 100$$

In high HIV-prevalence regions, co-infection rate may exceed 80%.

3. Functioning

To be complete, evaluation should also look at how well the project functions, particularly with respect to three aspects: *organization of care, established procedures,* and *human resources*.
A set of quality criteria is evaluated for each of these aspects. The criteria may be either qualitative (description) or quantitative (indicators). The table below can be used as a rough guide.

3.1. Organization

CRITERION	Quantitative and qualitative INDICATORS	GOAL
Patient comfort	– Patient welcome (condition of the facility, heating, etc.) – Food during hospitalization and/or for outpatients (supplemental rations, quantities, organization in charge) – Bed occupancy rate (BOR) of the TB ward	– According to needs – BOR ≤ 100 %
Hospital hygiene	– Equipment (gloves, gowns, autoclaves, medical equipment, cleaning supplies, etc.) – Waste management (sorting, incinerator, etc.)	All necessary equipment is available and used.
Information and therapeutic education	Patient interviews conducted	Patient autonomy (self-administered treatment)
Accessibility of care	Accessibility of treatment facilities, decentralization, etc.	Easy access to care during the intensive and continuation phases
Continuous supply of lab materials	– Supplied by (government agency or facility, other?) – Buffer stock – Number and duration of shortages	 – 3-month buffer stock – No shortages
Continuous supply of quality-assured anti-TB drugs	– Stock card maintenance – Order frequency, delivery delays, buffer stock – Shortage(s) – Drug sources – Institution in charge of supply – Use of FDCs – Storage conditions – Organization of supply	– Stock cards up-to-date – One person in charge of the pharmacy – Adequate frequency and buffer stock – No shortages – WHO-prequalified sources – Use of FDCs – Storage conditions appropriate – Regular supply of peripheral facilities

CRITERION	Quantitative and qualitative INDICATORS	GOAL
Case finding	– Type of case detection (active or passive) – Contacts screening? – Detection rate of new M+ cases – % smear-positive patients out of the total number of patients who had a sputum smear.	Know the type, in order to interpret the quantitative results of case finding – Yes – Depends on the context – < 20%
Diagnosis of M– and EP forms	– X-rays possible – Others (Rivalta, Pandy; FNAC) – Algorithm used	– Yes – Yes – Yes
Culture and DST	– Culture possible (methods, quality control) – DST possible (methods, quality control)	– Confirmation of failures – Improved diagnosis of M– and EP forms – Detection of resistance (in cases where treatment of resistant TB is possible)
Identification of non-adherent patients	– System for identifying and looking for non-adherent patients – % of patients who resumed treatment among those missing for less than 2 months who had to be looked for	– Yes – > 90%
Integrated TB/HIV care	– Access to voluntary counseling and testing (VCT) – Access to ART – Access to cotrimoxazole prophylaxis – TB treatment integrated in the HIV service, or HIV treatment in the TB service	– Yes – Yes – Yes – Yes

3.2. Procedures

CRITERION	Quantitative and qualitative INDICATORS	GOAL
Standard precautions (SP)	Description	SP followed
Registers and records (TB register, lab register, treatment card)	Description of the documents – Consistency between treatment cards and TB register – Consistency between TB register and lab register	Records reliable: – 100% – 100%

CRITERION	Quantitative and qualitative INDICATORS	GOAL
Standard case definitions	% patients with exact case definition out of the total number of patients included	– 100%
Adequate standard treatment regimens	– % new cases correctly treated (dosage, duration and anti-TB combinations) out of the total number of new patients treated – Ditto for re-treatments – % patients who did not have a sputum smear done at the end of the intensive phase out of the total number of patients who finished treatment – % patients who did not have a sputum smear done at month 5 out of the total number of patients who finished treatment	– > 90% – > 90% – < 10% – < 10%
Criteria for cure	– % of new M+ cases declared cured who actually had 2 negative smears (one at the end of treatment and one at least one month apart). – Ditto for re-treatments	– > 90% – > 90%
Quarterly monitoring	– Quarterly report on new cases and re-treatments – Quarterly cohort analysis	– Quantitative data on inclusions and results collected every 3 months – Rapid detection of potential problems
Adherence monitoring	– % patients coming in for their appointment out of number of patients expected Randomized study on a representative sample of patients: – Objective measures: lab analyses or urine colour – Subjective measures: patient report: % of patients who had taken their medication (correct dosage and schedule) for the last two days	– > 90% in both the intensive and continuation phases – > 90% – > 90%

CRITERION	Quantitative and qualitative INDICATORS	GOAL
Prevention of airborne transmission of *M. tuberculosis*	– Written prevention plan? – Person in charge identified? – Building ventilation, lights, UV lamps (hospital wards, outpatient clinics, laboratory); anti-inhalation masks for staff and visitors in contact with contagious patients; anti-projection masks for contagious patients (if they move about) – Isolation – Conversion rate – % M+ patients hospitalized in a non-TB ward, out of the total number of M+ cases.	– Yes – Yes – Appropriate use of means – Isolation of M+ patients – Isolation of DRM+ patients – > 80% – < 10%
Laboratory quality control	Regular evaluation of laboratory functioning Quarterly quality control of smear analysis and EQA (external quality assessment).	Ensure the quality of laboratory analyses for bacteriological TB diagnosis Reliability of results: – Overall concordance > 95% – % false negative ≤ 5% – % false positive = 0%

3.3. Human resources

CRITERION	Quantitative and qualitative INDICATORS	GOAL
Staff	Job descriptions (doctors, nurses, lab technicians, cleaning staff, etc.) Medical staff-to-patient ratio	On average: – One nurse for every 10 to 15 patients on treatment – One doctor for every 40 to 50 patients on treatment
Training	Refer to training programme evaluation criteria	Competent staff
Other contributors	Description of other contributors: other NGOs, local associations, etc.	

A grid for evaluating TB clinic operation can be found in Appendix 9.2. Each criterion is rated either "satisfactory" or "unsatisfactory."

Appendices

1 - Expected number of cases

The following are needed to calculate the expected number of cases: an *estimate of the annual risk of infection (ARI)* and the *population figure*.

It should be noted that this calculation is only acceptable for countries where TB prevalence is high, as well there being a high ARI.
Moreover, it does not take into account the influence of the prevalence of HIV infection on the incidence of TB, which can be significant in certain regions.

Example: Population: 175,000; ARI: 3%

– M+ incidence (iM+)/100,000/year: 55 x ARI = 55 x 3 = 165
– M+ incidence (iM+)/175,000/year: 1.75 x 165 = 269

– M+ prevalence/100,000: 2 x iM+ = 2 x 165 = 330
– M+ prevalence/175,000: 2 x iM+ = 2 x iM+ = 2 x 289 = 578

It can be expected, if all cases are detected, that approximately 48 new M+ cases per month will be identified (578 ÷ 12). The most active programmes rarely detect more than 70% of cases, so in this example a maximum figure of 30 to 35 new M+ cases per month may be considered a reasonable estimate.

In the same manner, the prevalence of pulmonary TBM– and EP forms may be estimated (= 1.2 x M+ prevalence).

It is necessary to take into account the fact that the number of detected cases may exceed the estimate if a certain number of cases that did not originate from the population from which the estimate was calculated are also included in the project. For example, this may be observed in a refugee camp where the project also accepts subjects from outside the camp.

2.1 - Sputum collection techniques

1 - Sputum obtained spontaneously

The quality of sample determines the reliability of the result. Check that the sample contains solid or purulent material and not only liquid and frothy saliva.

It is better to collect samples in the morning before the patient has eaten. However, if this is not the case and the patient has eaten, ask him to rinse his mouth with water in order to avoid the presence of food in the sputum sample.

The first specimen is collected on site (spot specimen), outside in the open air and far away from other people, either during the consultation or at the laboratory.
The second specimen is collected at home by the patient in the morning, before eating (supply a sputum container, and make sure the patient knows how to use it).
If a third specimen is to be collected at the laboratory when the patient brings the second specimen, it must be collected outside in the open air and far away from other people.

Sputum collection

– The patient must be given a labeled sputum container (or a Falcon® tube, if the sample is to be shipped by air).
– Have the patient take a deep breath, hold for a few seconds, exhale, repeat two or three times, then cough: sputum is material brought up from the lungs after a productive cough.
– Collect approximately 3 ml and close the container hermetically.

Any staff member present during sputum collection should wear a high filtration mask.
Always check the quality of the sample, and take a new sample if unsatisfactory.

2 - Gastric aspiration (only in order to perform cultures)

Gastric aspiration is sometimes used in children when sputa cannot be spontaneously expectorated nor induced using hypertonic saline.

Sputum collection

– Place the child in a half-sitting or sitting position. Insert a nasogastric tube and check that it is correctly placed.
– First suction to collect the gastric fluid and place it in the sputum container, then rinse the stomach with 30 ml of sterile water and suction again. Add the suctioned fluid to the first sample.
– Start culture within 4 hours of collecting the sample. If there will be more than four hours' delay, neutralize with 100 mg of sodium bicarbonate.

3 - Sputum induction (only in order to perform cultures)

Sputum induction is sometimes used in children when sputa cannot be spontaneously expectorated.
Sputum induction may provoke bronchospasm and must be performed under close medical supervision. The child should be observed for respiratory distress during and for 15 minutes after the procedure. If indicated, 2 puffs of salbutamol and oxygen may be given.

Equipment

- High filtration mask for the operator and for the carer
- Gloves
- Suction catheter (6, 7, 8F)
- Sputum container
- 50 ml syringe, needle
- Mask and tubing for nebulizer

(single use)

- Holding chamber with child's mask (sterilize between each patient)
- Sterile hypertonic solution of 5% sodium chloride (to be kept refrigerated)
- Sterile solution of 0.9% sodium chloride (for the specimen)
- Salbutamol spray
- Oxygen

Procedure

The child should fast for at least 2 hours before the procedure.

- Prior to nebulization:
  - Explain the procedure to the child and/or the person accompanying him.
  - Place the child in a sitting position in the adult's arms.
  - Administer 2 puffs of salbutamol via a holding chamber, 10 minutes before nebulization.
  - Prepare a sputum container.
- Nebulization:
  - Fill the nebulizer with 5 ml of 5% hypertonic saline solution (sputum inducer).
  - Don an anti-inhalation mask.
  - Place the nebulizer mask over the child's mouth.
  - Leave the child to inhale until the reservoir is empty.
- Nasopharyngeal suction (a young child does not expectorate spontaneously):
  - Do 1 to 2 minutes of clapping.
  - Clean out the nasal cavity.
  - During suction, the child is laid on his side, back to the operator, who is behind him.
  - Fit a suction catheter to a 50-ml syringe. Lubricate the end of the catheter.
  - Measure the distance from the tip of the nose to the angle of the jaw. Insert the suction catheter to that depth.
  - When inserting and withdrawing the tube, pull on the plunger of the syringe to create suction.
  - Once the syringe is filled with air and mucus, disconnect it from the suction catheter and purge the air (tip facing upward), so that only mucus is left in the syringe.
  - To collect the mucus: draw 2 ml of 0.9% saline into the syringe to rinse, then empty contents into the sample container.

2.2 - Storage and shipment of sputum specimens

1 - Storage

When microscopic examinations are not performed on the site of collection:

– If the specimen is for a sputum smear microscopy:
  • Keep the specimen at +4°C, protected from light.
  • Stain it within one week.
  Without respecting these precautions, the specimen will liquefy; bacilli will be still present but more difficult to stain.

– If the specimen is for a culture in liquid medium:
  • Keep the specimen at +4°C, protected from light.
  • The specimen should be cultured as soon as possible—there should be no more than 2 weeks between sputum collection and inoculation.

– If the specimen is for a culture on Lowenstein-Jensen medium:
  • Cethylpyrodinium chloride (CPC) is used as transport medium.
  • Keep the specimen at +4°C, protected from light.
  • The specimen should be cultured as soon as possible—there should be no more than 2 weeks between sputum collection and inoculation.

2 - Shipment

Shipping to a local laboratory

Sputum containers should be transported between 2° and 8°C.

Shipping by air to a reference laboratory for culture

Sputum samples are collected and shipped in 50-ml Falcon® conical tubes with screw caps. The tubes are transported at room temperature, labeled UN number 3373, corresponding to Category B Infectious Substances.

Samples are triple-packaged, in accordance with IATA Packing Instruction 650:

1. Primary container holding the sputum sample: tube tightly closed and placed into a latex glove.
2. Secondary container, intended to protect the primary container: leakproof box with enough absorbant material to absorb the entire sample, should the primary container break.
3. Outer packaging intended to protect the secondary container: reinforced cardboard box with UN 3373 labeling.

Information to be furnished:

– Primary container: label the tube with the patient's name or identification number and the sample collection date and location.
– Outer package: indicate the name of the receiving laboratory, the complete address (name, street, postal code, locality, country), and telephone number.
– All samples must be accompanied by the corresponding lab test request (including clinical information).

Note: procedures for shipping bacterial strains obtained after culture are different, more complicated, and rarely feasible in practice. Cultures are classified as Category A Infectious Substances (UN number 2814).

For a detailed description of the procedures, see MSF *Medical catalogue*, volume 4.

2.3 - Ziehl-Neelsen staining (hot method)

Equipment

– Gloves and high filtration mask
– Water, distilled or filtered
– Carbol fuchsin
– Acid-alcohol 3% (ethanol + hydrochloric acid)
– Methylene blue 0.3%

Staining procedure

– Flood the slide with carbol fuchsin (after filtering the carbol fuchsin)
– Gently heat the slide. Begin timing as soon as steam appears; let it steam for 5 minutes, without allowing the slide boil or dry out.
– Gently rinse the slide with distilled (or filtered) water until the water runs clear; drain.
– Cover the slide with 3% acid-alcohol solution, leave on for 3 minutes, then drain. Repeat this operation 2 or 3 times, until the slide is completely decolorized.
– Rinse the slide with distilled or filtered water, and drain.
– Cover the slide with methylene blue, and leave on for 1 minute.
– Gently rinse the slide with distilled or filtered water until the water runs clear, then allow to air dry.

Reading and reporting

A slide should be examined by an experienced laboratory technician on at least 300 fields (15 minutes on average) before giving a negative result. A technician can hardly read over 20-25 slides per day.
Tuberculosis bacilli stain red on a blue background, are straight or slightly curved, and often cluster in groups of 3 to 10.

Grading AFB scale (CDC-ATS)

Number of AFB	Report
0	Negative
1-2 per 300 fields	+/-
1-9 per 100 fields	+
1-9 per 10 fields	++
1-9 per 1 field	+++
More than 9 per 1 field	++++

In many countries, the WHO-IUATLD scale is used:

Grading AFB scale (OMS-UICTMR)

Number of AFB	Report
0 AFB per 100 fields	Negative
1-9 AFB per 100 fields *	Record exact figure
10-99 AFB per 100 fields	1+
1-10 AFB per field	2+
More than 10 AFB per field	3+

Equipment for sputum smear microscopy with Ziehl-Neelsen (ZN) method

Equipment and reagents may be ordered in the form of laboratory modules:
- EQUIPMENT FOR TUBERCULOSIS module
- TUBERCULOSIS REAGENTS module
- MICROSCOPE module

If the laboratory is already set up and does not have all of the equipment, it is possible to order item by item. Details of these kits are found in the MSF *Guide of kits*. Local supply of reagents is possible, but quality should be verified.

2.4 - Auramine stain

Equipment

– Gloves and high filtration mask
– Water, distilled or filtered
– Auramine O, 0.1% solution
– 0.5 % acid alcohol
– Potassium permanganate, 0.5% solution
– Fluorescence microscope (or a fluorescence device that can be attached to a standard light microscope)

Staining procedure

– Flood the smear with auramine 0.1% solution and allow staining for 15 minutes ensuring that smears remain covered with stain.
– Rinse with distilled or filtered water until water runs clear and drain excess water from the slide. Do not use water containing chlorine (risk of interference with the fluorescence).
– Flood the smear with 0.5% acid-alcohol for 2 minutes to decolorize it.
– Rinse with distilled or filtered water and drain excess water from the slide.
– Flood the smear with potassium permanganate 0.5% solution and allow to counterstain for 2 minutes. Time is critical because counterstaining for longer may quench the fluorescence of AFB.
– Rinse with distilled or filtered water and drain excess water from the slide. Wipe the back of the slide with tissue paper.
– Allow smears to air-dry. Read as soon as possible after staining

Note: to control the quality of the coloration, it is essential to include at least a known positive smear in the batch.

Reading and reporting

– Always read the positive control first. If the positive control smear is not positive, do not continue with the patient smears, but re-stain the batch.
– Look aspect of smear: black background without debris or artefacts.
– Read one length of the smear (about 40 fields):

Number of AFB	Report
0 AFB per 1 length	Negative
1-19 per 1 length	Report exact number
20-199 per 1 length	1+
5-50 per field	2+
More than 50 per field	3+

Caution:
– The technique need a skilled reader (artefacts are often frequent).
– The fluorescence stain remains stable only for 3 days when sheltered from light. QC has to be organised accordingly.

2.5 - Bleach sedimentation

Bleach sedimentation increases the sensitivity of microscopy.

Equipment

– 15 ml plastic conical screw capped tube
– 3.5% bleach solution (12° chl)[1]
– Vortex (optional)
– Transfer pipettes
– Slides

Technique

– Transfer the sputum to the 15-ml tube.
– Add an equal amount of 3.5% bleach.
– Screw the cap back tightly, shake vigorously until the mixture is homogeneous.
– Let stand for sedimentation at room temperature for 15 to 18 h.
– Using a pipette, carefully transfer the supernatant to a waste container containing a 1% chlorine solution.
– Mix the sediment with the remaining fluid,
– Transfer 2 drops of the sediment to a slide,
– Make a smear and let it air dry in a horizontal position,
– When the smear is completely dry, fix it by passing the smear through a flame 3 times.

[1] It is important to check the actual available chlorine content of the bleach with a pool tester.

2.6 - Protein estimation

1 - Pandy test

Pandy test is used to detect an increase of protein in the cerebrospinal fluid (CSF).
The normal range of protein in CSF is 0.20-0.45 g/l
The Pandy test is positive when protein is superior to 0.45 g/l.

Equipment

– Gloves
– Pandy reagent
– Pasteur pipettes
– Conical centrifuge glass tube or test tube
– 1 ml pipettes

To prepare 500 ml of Pandy reagent

Pandy is a saturated phenol solution.
– Wear gloves.
– Weigh 30 g of phenol and transfer it in a 1000 ml bottle.
– Add 500 ml of distilled water and shake vigorously.
– Leave to stand for one day.
– Check whether any phenol remains undissolved:
  If so filter, the solution is ready.
  If all the phenol has dissolved, add a further 10 g of phenol and wait another day before filtering.

Pandy reagent is a highly corrosive and toxic solution:
– Label the bottle and mark it corrosive and poisonous.
– Wash hands after the preparation.

Technique

– Place 1 ml of Pandy reagent in a centrifuge tube.
– Add 3 drops of CSF (drop by drop).
– After each drop, look for a white cloud in the tube.
– In order to facilitate the reading, place a black surface behind the tube.

Results

– Presence of a white precipitate: Pandy test positive
– Absence of a white precipitate: Pandy test negative

2 - Rivalta test

The Rivalta test is used to detect an increase of protein in the body fluid (ascites, pleural fluid, synovial fluid).
The test is positive when the proteins are superior to 30 g/l.

Equipment

– Gloves
– Rivalta reagent
– Pasteur pipettes
– Conical centrifuge glass tube or test tube
– 5 ml pipette

To prepare 100 ml of Rivalta reagent

– Place 50 ml of distilled water in a 100 ml measuring cylinder.
– With a 5 ml pipette, add 3 ml of glacial acetic acid and make up to the 100 ml mark with the remaining 50 ml of distilled water.
– Transfer the solution in a bottle.

Technique

– Place 2 ml of Rivalta reagent in a centrifuge tube.
– Add 3 drops of pleural/ascites fluid, drop by drop.
– After each drop, look for a white cloud in the tube.
– In order to facilitate the reading, place a dark surface behind the tube.

Results

– Presence of a white precipitate: Rivalta test positive
– Absence of a white precipitate: Rivalta test negative

2.7 - *P. westermanii*, direct examination

Aspect of sputum

The typical aspect is a brown red colour with rusty brown gelatinous particles.

Equipment

– Gloves
– Microscope (obj x10 and x40)
– Slide and cover slide
– Sodium hydroxide (NaOH)
– Wire loop (Pasteur handle)

Technique

– Wear gloves.
– With a wire loop transfer a rusty brown particle (when present) on a slide.
– Cover with a cover slide and press gently to have a thin spread smear preparation.

Results

Paragominus egg aspects:
– Shape: asymmetric with a flat operculum on one side
– Size: 80-100/50-65 µm
– Colour: yellow brown or brown

The technique is not very sensitive. Concentration in NaOH can be performed, especially when the sputum has no rusty brown particles.

2.8 - *C. neoformans*, india ink preparation

This test looks for the presence of *Cryptococcus neoformans* in CSF. *C. neoformans* is a yeast fungus surrounded by a large capsule.

Aspect of CSF

– Clear or slightly cloudy
– Numerous cells (mostly lymphocytes)

Equipment

– Gloves
– Microscope (obj x10 and x40)
– Slide and cover slide
– India ink
– Hand centrifuge

Technique

– Centrifuge the CSF for 10 minutes.
– Place one drop of India ink.
– Add one drop of CSF sediment on a microscope slide.
– Cover with a cover slide. Avoid apparition of air bubbles.

Results

Aspect of *Cryptococcus neoformans*: encapsulated, round yeast cell of 5-7 µm. The background is black, the yeast and capsule remain uncoloured.

2.9 - Fine needle aspirate cytology (FNAC)

FNAC is used to obtain material from lymph nodes. The material is expressed onto slides and prepared for examination.

Two smears will be prepared with Giemsa stain[2] to look for caseum, granuloma, giants cells, and epithelioid cells or histocytes and 1 or 2 will be prepared with ZN stain to look for AFB.

Equipment

– Needle 23 G (in very few cases, it would be possible to use 19G)
– 10 ml syringe
– 2 slides for Giemsa + 1 or 2 for ZN stain
– Polyvidone iodine, sterile gauze, gloves

Fine needle aspiration technique

– Disinfect the area.
– With the needle attached to the syringe, insert the needle deep into the lymph node.
– After the needle has entered the mass, pull back on the syringe plunger to create a vacuum.
– Rapidly move the needle in a to-and-fro fashion to allow material entering the needle.
– When blood or material appears in the needle hub the aspiration should be stopped. Try to aspirate as much as possible of materials, the amount of materials that has been aspirated would have effect on the specificity and sensitivity of diagnosis.
– Release the negative pressure before to take out the needle from the lymph node. Do not continue sucking while you are taking out the needle, like this you will avoid aspiration of materiel into the barrel of the syringe and avoid mixing the sample with the possible peripheral blood in the skin.

Slide preparation

Slide should be identified prior to the aspiration and prepared immediately after the aspiration.
– Detach the needle from the syringe immediately after the aspiration.
– Fill the syringe with air (needle is still detached).

Prepare the smear as follow:
– *Giemsa*
  • Reattach the needle to the syringe and carefully release one small drop of sample onto one end of the slide by pushing down the plunger of the syringe (if the drop is placed in the middle of slide it would be difficult to make smear afterwards).

[2] The golden standard of diagnosis for TB on tissue samples is hematoxylin-eosin stain, but Giemsa stain can be used as an alternative in remote areas with limited equipment.

- Put another slide over the sample.
- Slide the two slides against each other, in opposite directions, to spread the sample out completely between them. Do not press the slides together forcefully, to avoid crushing the cells.
- Allow to air dry.
- Fix the smears by methanol when they are completely dry.
- Proceed to Giemsa staining.

– *ZN*
  - Place a small drop of ganglion aspirate on the slide.
  - Make a smear that is neither to thin or too thick.
  - Allow to air dry.
  - Fix the smear by flame when it is completely dry.
  - Proceed to ZN staining.

Reading the slide after Giemsa staining

On each slide, one or several of the following aspects can be found:
– Caseation necrosis (caseum): a uniform, acellular, pinkish substance.
– Granuloma: cluster of epithelioid cells and lymphocytes scattered through out smear with or without caseous necrosis.
– Epithelioid cells: elongated, often semi-lunar cells with a fine granular nuclear chromatin surrounded by pink cytoplasm.
– Giant cells: huge multinuclear cells.

Notes:
– It would be better to look for granuloma and necrosis with the 10x and 40x power of microscope then to look for epithelioid cells and giant cells with 100x power.
– Observation of smear requires a competent reader with skills in cytology. Slides have to be sent to a referral cytopathology laboratory for quality control or confirmation.
– The quality of the specimen and the preparation are essential. The smear is to be done by skilled technicians.

2.10 - Bio-safety cabinet (BSC)

Class I BSC

A Class I BSC protects the operator and the environment from contamination by the material being manipulated inside the cabinet, but does not protect the material being manipulated from contamination by the ambient air.
The material being handled is not protected because the ambient air that enters through the front opening and circulates over the work surface is not filtered. Only the air exiting the cabinet is filtered through a HEPA[3] (High Efficiency Particulate Air) filter, in order to protect the environment.
As a result, these BSCs cannot be used to perform cultures.

Class II BSC

A Class II BSC protects not only the operator and the environment, but also the material being manipulated inside the cabinet.
The room air and the air circulating within the cabinet are drawn by a downward flowing current through a grate, then through a HEPA filter, which protects both the operator and the product. The air exiting the cabinet is filtered through a HEPA filter to protect the environment.
Class II BSCs are required for performing cultures.

[3] All BSC must be equipped with a HEPA filter to filter the air discharged from the cabinet. HEPA filters trap 99.97% of particles ≥ 0.3 μm.

2.11 - Quality assurance

Quality Assurance (QA) is a whole set of activities designed to continuously provide assurance that the techniques are correctly done (all steps from the sample collection to reporting result) and the results are accurate and reliable.

Quality assurance is composed of *quality control* and *external quality assessment*.

1 - Quality control (QC)

Includes all internal operational techniques or tasks that are in place to find and correct error sources that might occur at all stage of the activities. For instance: using positive and negative control slides to check the quality of the staining, confirm all positive slides by an other technician before the result is given out.

2 - External quality assessment (EQA)

Includes an on-site evaluation by a supervisor (expatriate or national) and an evaluation of reading of slides. Evaluation of reading of slides is done by comparing the results obtained in the laboratory for a panel of slides sent from a referral laboratory (panel testing or proficiency testing) and by blinded rechecking (slides sent from laboratory to referral laboratory).

2.1 - On-site evaluation

Checklists are used to perform during on-site evaluation. The number of criteria to be evaluated is given as an example. This checklist could be revised and enlarged by doing specific list (e.g. smearing, ZN stain, etc.).

	Yes	**No**
Sample quality		
Check the quality of the expectoration		
Refuse saliva and order an other specimen		
Use a correct container (disposable, rigid, cap closing hermetically)		

	Yes	No
Specimen identification		
Receipt a laboratory request form correctly filled with the specimen		
Give a laboratory identification number and report the request on the laboratory register		
Report the identification number on the slide and on the sputum container		
Specify the number of the sample (1 to 3)		
Safety and hygiene		
Wear an anti-inhalation mask, a laboratory coat, gloves		
Work in an appropriate area		
Sterilise loop correctly		
After preparation of TB slides, clean all work surface with a 1% chlorine solution		
Incinerate the sputum container after use		
Technique		
Smear correctly done (not too thin and small, not too thick)		
Smear correctly stain (report to the technical procedure)		
Reading		
Take 15 minutes to give a negative result		
Use a reference AFB grading scale (specify which one is used)		
Clean the microscope objective between each examination		
Report correctly the result on the request form and on the laboratory register		
QC and EQA		
Keep the slides for the quality control		
Quality control is done regularly		
Laboratory register		
The laboratory register is correctly filled		
It is in correlation with the TB register		
Stock management		
Laboratory has a sufficient stock of reagents and laboratory supplies		

2.2 - Panel testing

Panel testing (or proficiency testing) consists in sending a set of stained (or unstained) slides with known results from a reference laboratory to the laboratory that has to be evaluated. This method allows a rapid evaluation of the capacity of the lab technicians to perform AFB microscopy. The test panel is composed of slides with different grades of positivity.

2.3 - Blinded rechecking

Blinded rechecking should be done regularly in order to guarantee continuous reliability of results. Each quarter a representative number of slides, already read by technicians, should be verified. Slides have to be selected randomly and read blindly (the person responsible for rechecking should not know the result).

Analysing the results

Laboratory and control results are gathered in a control sheet.

Slides n°	Lab result	Control result	Remarks
1	neg	neg	
2	neg	+	False negative (FN)
3	++	++	
4	+	neg	False positive (FP), numerous artefacts, stain deposits
….			
58	neg	neg	
59	neg	neg	Smear too thin
60	+	+	

Then the number of false negative and false positive are summarized in one table.

	Verification +	Verification –	Total
Reading +	13 (TP)	1 (FP)	14
Reading –	2 (FN)	44 (TN)	46
Total	15	45	60

TP: True Positive / FN: False Negative / FP: False Positive / TN: True Negative

Percentage of FN: 2 ÷ 46 x 100 = 4.34%
This shows the proportion of slides controlled positive among the negative slides of the laboratory.

Percentage of FP: 1 ÷ 14 x 100 = 7.14%
This shows the proportion of slides controlled negative among the positive slides of the laboratory.

Overall agreement: (13 + 44) ÷ 60 x 100 = 95%
Overall agreement should be at least 95%.
Percentage of FN should be less or equal to 5%.
Percentage of FP should be 0%.

When controlling the result, an assessment of slide's smearing and staining is also performed, thus a percentage of "good quality slides" can be given.

Sample size

Different sampling methods exist. The objective is to do regular control and to give the results to the laboratory in a minimum of delay.
– One consists in controlling 100% of positive slides and 10% of negative slides. This method may represent (for laboratory with high activity) a high number of slides to be controlled. It can overwhelm the capacity of the controllers to check the slides and to give the results in a minimum delay.
– A smaller sample size can be used: 20 or 50% of positive and same number of negative slides.
– Some programmes use a sampling method based on the Lot Quality Assurance System (LQAS).

Example of LQAS sampling method

Different parameters have to be considered:

Slide Positivity Rate (SPR)
SPR = (Number of positive slides per year/Total number of slides per year) x 100
The number is calculated on the basis of the register of the previous year.

Total Negative Slides (TNS)
TNS = Total number of slides per year ? Number of positive slides per year

Sensitivity
Expected performance in detecting positive slides: TP/TP+FN
The level of acceptable sensitivity for established programs is 90%.

Specificity
Expected performance in detecting negative slides: TN/TN+FP
The level of acceptable sensitivity should be 100% (no FP).

Acceptance number
Maximum number of errors allowed before action is taken. Choosing 0 will keep the sample size small but one error found will be a sign of a problem; if the acceptance number is 1, one error will not be an indication of a big problem.

Requirements
– Save all slides after cleaning them with xylene. Store them in slide boxes in the same order they are listed in the laboratory register.
– Slides must be randomly selected, and in sufficient number.
– Slides must be sent quarterly to the reference laboratory.

– Re-examination must be blinded (original results must not be known).
– Feedback of the results to the peripheral laboratories is essential.
– Investigate potential sources of errors during on-site evaluation.
– Provide remedial training or other corrective measures.

The following table gives the Recommended Annual Sample Size
(for a sensitivity of 90%, a specificity of 100%, an acceptance number of 0, and 95% confidence interval)

		Slide Positivity Rate (SPR)													
		2.5%	**5%**	**7.5%**	**10%**	**13%**	**15%**	**18%**	**20%**	**23%**	**25%**	**28%**	**30%**	**33%**	**35%**
Total number of negative slides	**100**	93	86	82	78	71	68	65	61	58	56	53	51	48	46
	200	168	146	130	118	102	94	88	81	74	71	65	61	57	55
	300	232	189	162	143	120	109	99	90	82	77	71	66	61	58
	400	285	223	185	160	130	118	106	96	87	81	74	69	63	60
	500	330	249	202	172	138	124	111	100	90	83	75	70	64	62
	700	404	288	227	189	148	132	117	104	94	87	78	71	66	63
	1000	486	326	249	203	156	139	122	108	96	88	79	73	67	63
	2000	637	386	281	223	168	147	128	113	100	92	82	76	69	65
	5000	783	434	305	238	175	153	132	116	103	93	83	77	70	66
	10000	847	453	314	242	178	154	133	118	103	93	83	77	70	66
	20000	883	462	318	246	179	155	134	118	103	95	85	77	70	66
	50000	907	468	321	247	179	156	134	118	104	95	85	77	70	66

3 - List of anti-TB medicines prequalified by the WHO

(see http://apps.who.int/prequal/)

Therapeutic area	INNic	Formulation and strength	Applicant	Manufacturing site	Packaging	Reference	Date of PQ
TB	Ethambutol	Tablets 400mg	Cadila Pharmaceuticals Ltd	Dholka, Ahmedabad, India	Blister 10; HDPE bottle 1000	TB008	2003-Nov-13
TB	Ethambutol	Tablets 400mg	Macleods Pharmaceuticals Ltd	Kachigam, Daman, India	Blister 10, 28; HDPE bottle 1000	TB134	2007-Mar-23
TB	Ethambutol Hydrochloride+Isoniazid+Pyrazinamide+Rifampicin	Film-coated tablets 275mg+75mg+400mg+150mg	Macleods Pharmaceuticals Ltd	Kachigam, Daman, India	LDPE bag in sealed Alu sachet further packed in HDPE container 500, 1000	TB168	2008-Mar-07
TB	Ethambutol+Isoniazid	Tablets 400mg+150mg	Macleods Pharmaceuticals Ltd	Kachigam, Daman, India	Blister 10, 28; HDPE bottle 1000	TB157	2007-Mar-23
TB	Ethambutol+Isoniazid+Pyrazinamide+Rifampicin	Tablets 275mg+75mg+400mg+150mg	Wyeth Pakistan Ltd	Karachi, Pakistan	Blister 80	TB024	2003-Nov-13
TB	Ethambutol+Isoniazid+Pyrazinamide+Rifampicin	Tablets 275mg+75mg+400mg+150mg	Lupin Ltd	Aurangabad, India	Blister 4; HDPE bottle 100, 500, 1000	TB070	2003-Nov-13
TB	Ethambutol+Isoniazid+Pyrazinamide+Rifampicin	Tablets 275mg+75mg+400mg+150mg	Sandoz Pty Ltd	Strides Arcolab, Bangalore, India; Sandoz Pty Ltd, Kolshet, Thane, India	Blister 10; PP bottle 1000	TB090	2004-Sep-14
TB	Ethambutol+Isoniazid+Rifampicin	Tablets 275mg+75mg+150mg	Macleods Pharmaceuticals Ltd	Kachigam, Daman, India	Triple laminated LDPE/PET/AL bag further packed in HDPE container 1000	TB183	2008-Oct-22
TB	Isoniazid	Tablets 100mg	Macleods Pharmaceuticals Limited	Kachigam, Daman, India	LDPE bag further packed in HDPE container 1000; PVC/PVdC/Alu blister 10	TB178	2008-Apr-23
TB	Isoniazid	Tablets 300mg	Macleods Pharmaceuticals Limited	Kachigam, Daman, India	LDPE bag further packed in HDPE container 1000; PVC/PVdC/Alu blister 10	TB179	2008-Apr-23

Therapeutic area	INNic	Formulation and strength	Applicant	Manufacturing site	Packaging	Reference	Date of PQ
TB	Isoniazid+Pyrazinamide+Rifampicin	Dispersible tablets 30mg+150mg+60mg	Macleods Pharmaceuticals Limited	Kachigam, Daman, India	Triple laminated LDPE/PET/AL bag further packed in HDPE container 1000	TB180	2009-Mar-03
TB	Isoniazid+Rifampicin	Tablets 75mg+150mg	Lupin Ltd	Aurangabad, India	Blister 15; HDPE bottle 100, 500, 1000	TB068	2003-Dec-19
TB	Isoniazid+Rifampicin	Tablets 150mg+300mg	Sandoz Pty Ltd	Novartis, Kempton Park, South Africa	Blister 10; PP bottle 20, 40, 60, 500	TB084	2003-Nov-13
TB	Isoniazid+Rifampicin	Tablets 75mg+150mg	Sandoz Pty Ltd	Strides Arcolab, Bangalore, India; Sandoz Pty Ltd, Kolshet, Thane, India	Blister 10; PP bottle 1000	TB085	2004-Sep-14
TB	Isoniazid+Rifampicin	Film-coated tablets 75mg+150mg	Macleods Pharmaceutical Ltd	Kachigam, Daman, India	PET/Alu/LLDPE triple laminated sachet further in HDPE container 500, 1000	TB158	2008-Mar-07
TB	Isoniazid+Rifampicin	Dispersible tablets 30mg+60mg	Macleods Pharmaceuticals Limited	Kachigam, Daman, India	Triple laminated LDPE/PET/AL bag further packed in HDPE container 1000	TB181	2009-Mar-03
TB	Isoniazid+Rifampicin	Dispersible tablets 60mg+60mg	Macleods Pharmaceuticals Ltd	Kachigam, Daman, India	Triple laminated LDPE/PET/AL bag further packed in HDPE container 1000	TB182	2009-Nov-09
TB	Pyrazinamide	Tablets 400mg	Cadila Pharmaceuticals Ltd	Dholka, Ahmedabad, India	Blister 10; HDPE bottle 1000	TB015	2003-Nov-13
TB	Pyrazinamide	Tablets 400mg	Macleods Pharmaceuticals Ltd	Kachigam, Daman, India	HDPE bottle 1000	TB159	2007-Mar-23
TB	Pyrazinamide	Tablets 400mg	Micro Labs Limited	Hosur, Tamilnadu, India	PE bag further packed in HDPE container 1000	TB171	2009-Jun-29
TB	Pyrazinamide	Tablets 500mg	Micro Labs Limited	Hosur, Tamilnadu, India	PE bag further packed in HDPE container 1000	TB172	2009-Jun-29

4 - Daily doses of anti-TB drugs

1 - Category 1 regimens (with FDC)

	Intensive phase	Continuation phase
TB M+, M–, EP	2 HRZE	4 HR
Meningitis (EP)	2 SHRZ	4 HR

Regimen **2 HRZE/4 HR**

Patients ≤ 20 kg (paediatric FDC)

Weight in kg	**5 - 7**	**8 - 14**	**15 - 20**
Intensive phase			
2 HRZE tab H 30 mg, R 60 mg, Z 150 mg	1	2	3
+ tab H 60 mg, R 60 mg	1	1	2
+ tab E 100 mg	1	2	3
Continuation phase			
4 HR tab H 30 mg, R 60 mg	1	2	3
+ tab H 60 mg, R 60 mg	1	1	2

Patients > 20 kg (adult FDC)

Weight in kg	**21 - 29**	**30 - 34**	**35 - 39**	**40 - 49**	**50 - 54**	**55 - 64**	**65 - 70**	**> 70**
Intensive phase								
2 HRZE tab H 75 mg, R 150 mg, Z 400 mg, E 275 mg	2	2	2 1/2	3	3	4	4	5
+ tab H 60 mg, R 60 mg	2	–	–	–	–	–	–	–
Continuation phase								
4 HR tab H 75 mg, R 150 mg	2	2	3	3	3	4	4	5
+ tab H 60 mg, R 60 mg	2	–	–	–	–	–	–	–

Regimen **2 SHRZ/4 HR**

Patients ≤ 20 kg (paediatric FDC)

Weight in kg	**5 - 7**	**8 - 14**	**15 - 20**
Intensive phase			
2 SHRZ tab H 30 mg, R 60 mg, Z 150 mg	1	2	3
+ tab H 60 mg, R 60 mg	1	1	2
+ *injectable S, in g*	*0.2**	*0.2**	*0.3**
Continuation phase			
4 HR tab H 30 mg, R 60 mg	1	2	3
+ tab H 60 mg, R 60 mg	1	1	2

** See [3 -] for dilution of streptomycin*

Patients > 20 kg (adult FDC)

Weight in kg	**21 - 29**	**30 - 34**	**35 - 39**	**40 - 49**	**50 - 54**	**55 - 64**	**65 - 70**	**> 70**
Intensive phase								
2 SHRZ tab H 75 mg, R 150 mg, Z 400 mg	2	2	2 1/2	3	3	4	4	5
+ tab H 60 mg, R 60 mg	2	–	–	–	–	–	–	–
+ *injectable S, in g*	*0.5**	*0.5**	*0.6**	*0.8**	*0.9**	*1**	*1**	*1**
Continuation phase								
4 HR tab H 75 mg, R 150 mg	2	2	3	3	3	4	4	5
+ tab H 60 mg, R 60 mg	2	–	–	–	–	–	–	–

** See [3 -] for dilution of streptomycin*

2 - Category 2 regimen (with FDC)

TB M+, M–, EP (except lymph node TB)		
	Intensive phase	**Continuation phase**
If **less than 5 months** of **E** during previous treatment	2 SHRZE/1 HRZE	5 HRE
If **more than 5 months** of **E** during previous treatment	2 SHRZE/1 HRZE	5 HRZE

Regimen **2 SHRZE/1 HRZE/5 HRE**

Patients ≤ 20 kg (paediatric FDC)

Weight in kg	**5 - 7**	**8 - 14**	**15 - 20**
Intensive phase			
2 SHRZE tab H 30 mg, R 60 mg, Z 150 mg	1	2	3
+ tab H 60 mg, R 60 mg	1	1	2
+ tab E 100 mg	1	2	3
+ *injectable S, in g*	*0.2**	*0.2**	*0.3**
1 HRZE tab H 30 mg, R 60 mg, Z 150 mg	1	2	3
+ tab H 60 mg, R 60 mg	1	1	2
+ tab E 100 mg	1	2	3
Continuation phase			
5 HRE tab H 30 mg, R 60 mg	1	2	3
+ tab H 60 mg, R 60 mg	1	1	2
+ tab E 100 mg	1	2	3

** See [3 -] for dilution of streptomycin*

Patients > 20 kg (adult FDC)

Weight in kg	**21 - 29**	**30 - 34**	**35 - 39**	**40 - 49**	**50 - 54**	**55 - 64**	**65 - 70**	**> 70**
Intensive phase								
2 SHRZE tab H 75 mg, R 150 mg, Z 400 mg, E 275 mg	2	2	2 1/2	3	3	4	4	5
+ tab H 60 mg, R 60 mg	2	–	–	–	–	–	–	–
+ *injectable S, in g*	*0.5**	*0.5**	*0.6**	*0.8**	*0.9**	*1**	*1**	*1**
1 HRZE tab H 75 mg, R 150 mg, Z 400 mg, E 275 mg	2	2	2 1/2	3	3	4	4	5
+ tab H 60 mg, R 60 mg	2	–	–	–	–	–	–	–
Continuation phase								
5 HRE tab H 75 mg, R 150 mg	2	2	3	3	3	4	4	5
+ tab H 60 mg, R 60 mg	2	–	–	–	–	–	–	–
+ tab E 400 mg	1	1 1/2	1 1/2	2	2 1/2	3	3	3 1/2

** See [3 -] for dilution of streptomycin*

3 - Daily dose and dilution of streptomycin

Streptomycin (vial of 1 g) is a powder for injection to be dissolved in sterile water for injection.

In children under 20 kg, dilute 1 g (one vial) in 10 ml of water for injection:

Weight in kg	≤ 7	8 - 14	15 - 20
Dose in g	0.2*	0.2*	0.3*
Dose in ml	2 ml	2 ml	3 ml

In children over 20 kg and adults, dilute 1 g (one vial) in 5 ml of water for injection:

Weight in kg	21 - 29	30 - 34	35 - 39	40 - 49	50 - 54	≥ 55
Dose in g	0.5*	0.5*	0.6*	0.8*	0.9*	1*
Dose in ml	2.5 ml	2.5 ml	3 ml	4 ml	4.5 ml	5 ml

⚠ Streptomycin is contra-indicated in pregnant women.

4 - Isoniazid prophylaxis in newborns and children

Weight in kg	< 3,5	3,5 - 5	6 - 9	10 - 15	16 - 20
tab H 100 mg	–	1/2	1	1 1/2	2
syrup H 50 mg/5 ml	3 ml	5 ml	9 ml	–	–

5 - First medical order

The quantities to be ordered depend on the number of expected patients.

Drugs

Fixed-dose combinations (FDC)

Always choose FDC. The order includes:

– A combination of 4 anti-TB drugs:
HRZE adult dosage (H 75 mg + R 150 mg + Z 400 mg + E 275 mg)
This combination is not available in paediatric dosage.

– A combination of 3 anti-TB drugs:
HRZ adult dosage (H 75 mg + R 150 mg + Z 400 mg)
and
HRZ paediatric dosage (H 30 mg + R 60 mg + Z 150 mg)

– A combination of 2 anti-TB drugs:
HR adult dosage (H 75 mg + R 150 mg)
and
HR paediatric dosages (H 30 mg + R 60 mg) and (H 60 mg, R 60 mg)

Single medications

– For children less than 25 kg, ethambutol (E) 100 mg paediatric tablets must be ordered to complete the paediatric fixed-dose combination (H 30 mg + R 60 mg + Z 150 mg).

– For the continuation phase of Category 2 regimens with HRE, ethambutol (E) 400 mg tablets must be ordered to compete the fixed-dose combination (H 75 mg + R 150 mg).

– Single medications must be ordered for 2% of patients in the event of intolerance to one of the ingredient included in FDC.

– Two-thirds of M+ patients are estimated to have at least one child requiring isoniazid prophylaxis for 6 months. Isoniazid (H) must be ordered in 100 mg scored tablet or in 50 mg/5 ml syrup.

– Streptomycin is an injectable drug, it never comes in FDC.

– Pyridoxine (vitamin B6) must be ordered in order to prevent and treat isoniazid-related neuropathy.

– Phytomenadione (vitamin K) must be ordered for pregnant women receiving rifampicin (as well as for newborns).

The basic principle is that one should never run out of stock. When in doubt, overestimate the quantities at the time of ordering. Doses are ordered for adults weighing 40 to 50 kg, and children weighing 15 to 20 kg.

The entire treatment is ordered for each patient, whether the duration of treatment.

In order to build and maintain a buffer stock, order for extra patients. For example, if 50 patients are expected in 6 months and 3 months' buffer stock is desired, add 25 patients to the order.

In the Excel TB order spreadsheet attached in the CD-ROM, indicate the number of patients for each treatment regimen, the quantities to be ordered will be calculated automatically.

Supply and equipment

Add the necessary drugs (e.g. antibiotics for common infections), supplies (e.g. spinal needles, masks, laboratory supplies and reagents) and equipment.

6 - Informing the patient and monitoring adherence

1 - At the start of treatment

Arrange two interviews (allow about 20 minutes for each): one to supply the patients with the information they need to follow the treatment, the second to make sure they have assimilated the information. These interviews should coincide with the first clinical visits. Depending on how the clinic is organized, the interviews are done either by the prescribing clinician alone at the time of the clinical visit, or with the help of a specially-trained staff member at an interview just for this purpose. The patient may bring someone else with him, if he likes.

Outpatients

First interview:

– Explain:
  - The disease and how it spreads:
    For example: this is a serious, but generally curable, infection, that affects the lungs and can be spread if not treated (tailor the information according to the focus of the infection).
  - The treatment process:
    Length, intensive/continuation phases, clinical and bacteriological monitoring, visit schedule (tailor the information according to the treatment category).
  - The medications:
    - Management:
      Where, when, and from whom to get medications
      Number of tablets/day, taken once a day on an empty stomach
      Keep tablets in their blister pack until taken, no removing them from their package ahead of time
    - Main adverse effects and what to do if they occur:
      For example: for rifampicin, point out that it turns the urine, stools, and tears reddish-orange, that this is normal and not a cause for concern. For ethambutol, advise patient to consult the doctor immediately if he notices a decrease in his vision or ability to correctly distinguish colours, etc.
    - Special precautions (depending on concomitant treatment):
      For example: take TB medications in the morning, and fluconazole at night.

– Answer any questions.

– Stress the importance of adherence, anticipate problems, and think about possible solutions.

– Give the date of the second interview (one week later).

Second interview (one week later):

– Check to make sure that information has been assimilated; ask open-ended questions, give the patient time to answer. Give more information, if necessary.
– Remind the patient of the date of the next visit.

Hospitalized patients

First interview:

Same as above, plus:

– Hospital infection control measures:
Isolation, for M+ PTB patients: covering the mouth when coughing or sneezing, use of spittoons, visits outside the building, masks (who, when, why), airing out the room, etc.
– Timetable for injections and distribution of drugs.

Second interview (at discharge):

– Preparation for returning home (where and when to get medications, visit schedule, importance of adherence, etc.)
– Make sure that the information the patient needs to continue treatment as an outpatient has been assimilated (treatment process, medications, adverse effects and what to do, etc.). Give more information, if necessary.
– Answer the patient's questions.

2 - In the course of treatment

The purpose of these interviews is to assess adherence throughout the entire course of treatment, and to identify/resolve any problems. Assessment is done either by the clinician at the monthly clinical visit, or by the nurse responsible for individual distribution of drugs. Adherence assessment should be quick (about 5 minutes); on the other hand, devote as much time as necessary to resolving any problems.

The interview at the end of the intensive phase is more specifically devoted to informing the patient, because of the changes in drug regimen for the continuation phase.

7 - Masks

Mask high filtration PCM2000 non sterile, single use

Mask covering the lower part of the face (nose, mouth, chin), equipped with a maximum water/air tightness and an effective filter, *preventing the inhalation of droplets*:

- for all persons in contact with contagious TB patients
- when collecting sputum samples and preparing slides, and when collecting and disposing of sputum containers.

Instructions for use

- Open the mask
- Bend the nasal bar
- Separate the straps using the two index fingers
- Lightly stretch the two straps
- Put the chin into the mask
- Stretch the two straps over the head
- Put the first strap at neck-height and the second strap on top of the head
- Mould the bar perfectly and adjust the mask while checking its tightness

Safety instructions

- The mask must be replaced at least every 3 hours
- It must be immediately replaced if it is damaged or contaminated by a body fluid or if respiratory resistance increases (= respiratory difficulties)
- Wash your hands after removing the mask

Storage

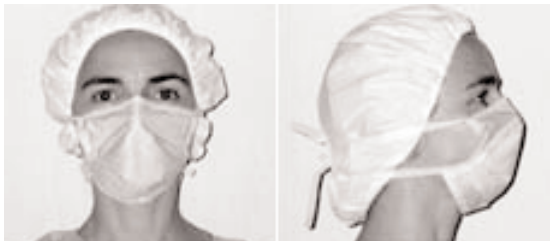
In a dry and well ventilated place.

Specifications

- Meets the specifications of the american norm N95
- Filtration level > 95% for particles from 0.1 to 0.3 µ
- Resistance to passage of air = 2.08 mm H_2O
- Tests conducted with particles of 0.3 microns

Alternative: mask without respiratory valve, meeting the EN 149 standard, class P2. The N95 american standard has as demanding specifications as the class P2 of the EN 149 standard.

Surgical mask non sterile, single use



Mask covering the lower part of the face (nose, mouth, chin), *preventing the emission of droplets* by contagious TB patients.

Instructions for use

- Open the mask
- Bend the nasal bar
- Separate the straps using the two index fingers
- Lightly stretch the two straps
- Put the chin into the mask
- Stretch the two straps over the head
- Put the first strap at neck-height and the second strap on top of the head
- Mould the bar perfectly and adjust the mask while checking its tightness

Safety instructions

- The mask must be replaced at least every 3 hours

Storage

In a dry and well ventilated place.

Specifications

- Holds particles larger or equal to 1 µ
- Filtration level > 95% for particles of 1 µ
- Filtering capacity kept for 5 hours, even in a humid environment

Masks made of woven fabric, compresses or one layer of paper are ineffective and must be proscribed.

8 - BCG vaccine

Composition, presentation and route of administration

– Live attenuated bacterial vaccine, for intradermal injection
– Powder for injection (lyophilised vaccine), to be dissolved with the entire vial of the specific solvent supplied by the manufacturer, in multidose vial

Dosage and vaccination schedule

– Child: 0.05 ml as a single dose as soon after birth as possible
– If child is over one year old: 0.1 ml as a single dose

Technique

– Clean the injection site with boiled and cooled water, do not use antiseptics (risk of inactivation of live vaccine), allow to dry.
– Administer the vaccine intradermally: if the injection is correctly done, it should provoke an "orange skin" papula, 5-8 mm in diameter.
– Administer the vaccine into the external face of the left arm, just above the attachment point of the deltoid. The vaccine is injected in the same place for all children to make it easy to find the BCG scar subsequently.

Contra-indications

– Do not administer to patients with congenital or acquired immunodeficiency (HIV infection, immunosuppressive therapy, etc.), malignant haemopathy.
– Vaccination should be postponed in the event of extensive acute dermatosis, acute complicated malnutrition (BCG will be given at the discharge from the nutritional centre), severe acute febrile illness (minor infections are not contra-indications).

BCG is not contra-indicated in asymptomatic HIV+ infants in countries with high TB prevalence.

Adverse effects

– These adverse effects necessitate no specific treatment, the evolution is almost always favourable:
  • normal local reaction 2 to 4 weeks after injection: papule which changes to an ulcer that usually heals spontaneously (dry dressing only) after 2 to 3 months, leaving a permanent scar;
  • persistent ulcer, characterised by serous discharge persisting for over 4 months after injection;
  • non-suppurated adenitis, most often axillary, sometimes cervical; cheloid scars;
  • abscess at the injection site, due to common germs (red, hot and painful abscess) or poor manipulation during injection or a vaccine with too high a dose (cold and painless abscess).

– Atypical complications:
  • suppurative adenitis, usually due to a vaccine with too high a dose, mostly observed in newborn infants. This lymph node, with a diameter at times over 3 cm, evolves toward softening and fistulisation with chronic suppuration. The best approach is to puncture the collected abscess with a needle in such a manner as to avoid fistulisation, followed by a single instillation into the cavity with a sterile solution of isoniazid or rifampicin. If fistulisation has already occurred, daily dressing with or without anti-TB drugs is sufficient, leading to a cure in a few weeks.
  • osteomyelitis due to BCG (in exceptional cases).

Precautions

– Do not mix with other vaccines in the same syringe (inactivation of vaccines).
– If administered simultaneously with EPI vaccines, use different syringes and injection sites.
– *Pregnancy: CONTRA-INDICATED*
– *Breast-feeding: no contra-indication*

Storage: 

– *Reconstituted vaccine: between 2°C and 8°C for 4 hours maximum, protected from light.*
– *Powder: between 2°C and 8°C, protected from light. Freezing is possible but unnecessary.*
– *Solvent: a cold chain is not required for storage. However, at least 24 hours before reconstitution of the vaccine, the solvent must be refrigerated between 2ºC and 8ºC so that the solvent and lyophilised powder are at the same temperature: a temperature difference during reconstitution may reduce vaccine efficacy. Do not freeze.*

QUATERLY REPORT

Case finding

Cohort N°: - - - - - **…quarter 200…**

Doctor: - - - - -

Date: - - - - -

H prophylaxis (children) started this quarter	M	F

Pulmonary TBM+

New cases	Relapses	Failures	TAI*	Others	TOTAL Male	TOTAL Fem.	TOTAL Total	Default before Rx NC	Default before Rx Re-Rx	Default before Rx Total

Pulmonary TBM-

New cases	Relapses	Failures	TAI*	Others	TOTAL Male	TOTAL Fem.	TOTAL Total	Default before Rx NC	Default before Rx Re-Rx	Default before Rx Total

Extrapulmonary TB

New cases	Relapses	Failures	TAI*	Others	TOTAL Male	TOTAL Fem.	TOTAL Total	Default before Rx NC	Default before Rx Re-Rx	Default before Rx Total

TOTAL Male	TOTAL Fem.	TOTAL Total	TOTAL NC	TOTAL Re-Rx	TOTAL Total
0	**0**	**0**	**0**	**0**	**0**

* TAI : Treatment After Interruption

	Age group <5 yrs	5-14 yrs	>14 yrs
Pulmonary TB M+			
Pulmonary TB M-			
Extrapulmonary TB			
Meningitis			
Miliary			
Pott's disease			
Other TB of bones			
Abdominal			
Pleural			
Lymph node TB			
- - - - - -			
TOTAL	0	0	0

Conversion rate in patients from previous quarter (NC M+)	……% (#/#)

QUATERLY REPORT

Treatment results

Cohort N°:……. **….quarter 200...** **TB centre: ……**

	Case definitions	Cured	Rx completed (no smear results)	Deaths	Failures	Treatment interrupted (default)	Transferred to another district	Treatment adapted*	Total number of cases
Pulmonary TB M+	New case								0
	Failure								0
	Relapse								0
	TAI								0
	Other								0
	Total PTB M+	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Pulmonary TB M-	New case								0
	Failure								0
	Relapse								0
	TAI								0
	Other								0
	Total PTB M-		**0**	**0**	**0**	**0**	**0**	**0**	**0**
Extrapulmonary TB	New case								0
	Failure								0
	Relapse								0
	TAI								0
	Other								0
	Total EP TB		**0**	**0**	**0**	**0**	**0**	**0**	**0**
Total and rates	**Total number**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Rates all TB	**#DIV/0!**		**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**
	Rate M+	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
	Rate M-		#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
	Rate EP		#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
	Total number re-Rx	0	0	0	0	0	0	0	0
	Rate re-Rx	#DIV/0!		#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!

* only for projects with DR-TB treatments

Among the same cohort of TB patients

Known HIV status	
HIV+	
Cotrimoxazole prophylaxis	

9.2 - Check-list for the evaluation of the functioning of a TB service

Date: Performed by:	
Organization	
Patient confort	
Hospital hygiene	
Patient information and therapeutic education	
Accessibility of care	
Laboratory supply	
Supply of quality-assured anti-TB drugs	
Case finding	
Diagnosis of M– and EP forms	
Cultures and DST	
Identification of non-adherent patients	
Integrated TB/HIV care	
Procedures	
Standard precautions	
Registers and patient records	
Standard case definitions	
Adequate standard treatment regimens	
Criteria for cure	
Quarterly monitoring	
Adherence monitoring	
Prevention of airborne transmission of *M. tuberculosis*	
Laboratory quality assurance	
Human resources	
Staff	
Training	
Other contributors	

10.1 - Request forms

REQUEST FORM FOR SPUTUM SMEAR MICROSCOPY

Treatment centre_____ Date _____

Patient information

Name _____

Surname_____ Sex_____ Age_____

Indication

Diagnosis _____ ☐

Follow-up _____ ☐ TB register number _____

Name and signature of requester _____

RESULTS

To be completed by the laboratory

Laboratory serial number _____

Dates	**Specimen**	**Appearance***	**Results** (Ziehl-Neelsen staining)**					
			negative	+/-	+	++	+++	++++
	1							
	2							

** blood-stained, mucopurulent, saliva*

*** results (CDC scale):*

neg : 0

+/- : 1-2 AFB per 300 fields (scanty)

+ : 1-9 AFB per 100 fields

++ : 1-9 AFB per 10 fields

+++ : 1-9 AFB per 1 field

++++ : more than 9 AFB per 1 field

Date _____ Examination performed by _____

REQUEST FORM FOR SPUTUM CULTURE

Always send 2 samples (A and B). Fill in one request form for each patient.

Treatment centre _____

Address _____

_____

Patient information

TB register number _____ Date registration _____

Name _____

Surname _____ Sex _____ Age _____

Indication

Diagnosis (M–) ..... ☐

Confirmation of failure..... ☐

DST for adapted regimen ..... ☐

Case definition

Suspect..... ☐

New ..... ☐

Re-treatment ..... ☐

Failure ..... ☐

Relapse..... ☐

TAI..... ☐

Other ..... ☐

Sputum

Baseline ☐

Follow-up ☐ Month N° _____

Current regimen _____

Results of microscopy performed in the treatment centre

TB laboratory number _____ Date _____

☐ scanty ☐ 1+ ☐ 2+ ☐ 3+ ☐ 4+ ☐ negative

Sputum specimen

Sample number _____ Date collection specimen A _____

Date collection specimen B _____

Request for culture and:

– DST for first-line drugs:

Yes ☐

No ☐

– DST for second-line drugs:

Yes ☐

No ☐

Date of shipment _____ Name and signature of requester _____

10.2 - Laboratory registers

Register for sputum smear microscopy

Lab serial N°.	Date	Name (in full)	Sex M/F	Age	Treatment centre	Patient's address	Reason for examination		Results of sputum specimen			Signature	Remarks
							Diagnosis	Follow-up	1	2	3		

Register for culture

Lab serial N°.	Date	Name (in full)	Sex M/F	Age	Treatment centre	Patient's address	Results		Colony morpho-logy	Growth rate	Niacin	Catalase	Ziehl-Neelsen confirmation	Signature	Remarks
							SSM	Culture			Nitrate	PNB			

SSM: sputum smear microscopy

Register for DST

Lab. serial n°	Date inoculation	Date reading	DST results (R/S)*										Signature	Remarks
			H	R	E	S	Z	Ofx	Km	Cm	Eto	PAS		

* R: resistant; S: susceptible

10.3 - TB register

Date Rx. start	District TB N°	Name	Sex M/F	Age	Address	Treatment category*	Disease site P/EP**	Type of patient***					
								N	R	F	D	T	O

* **Enter the treatment category**: CAT I: New smear-positive, smear-negative or EP. Specify treatment regimen: e.g. 2(HRZE)/4(HR)
CAT II: Re-treatment e.g. 2S(HRZE)/1(HRZE)/5(HRE)

** **Indicate the site of the disease**: P = pulmonary; EP = extrapulmonary

*** **Tick only one column**: N= New; R= Relapse; F= Treatment after Failure; D= Return after Default; T= Transfer in; O= Others

Results of sputum examination																Treatment outcome		TB/HIV activities			Remarks
At treatment start				2 or 3 months				4 or 5 months				End of treatment				Date	Outcome in text*	HIV** test Result date	ART Y/N Start date	CPT Y/N Start date	
Direct smear result	Date/ lab n°	Culture result	Date/ cult. n°	Direct smear result	Date/ lab n°	Culture result	Date/ cult. n°	Direct smear result	Date/ lab n°	Culture result	Date/ cult. n°	Direct smear result	Date/ lab n°	Culture result	Date/ cult. n°						

* **Treatment result**: Cured, Treatment completed, Failure, Death, Default, Treatment adapted, Transfer out

** **HIV test result**: Pos = positive (indicate Fuchia number), Neg = negative, UN = unknown

ART: Anti-retroviral treatment

CPT: Cotrimoxazole prophylaxis treatment

10.4 - TB treatment card

Tuberculosis treatment card

Name: _____

Address: _____

_____

_____

Age: _____ Sex: _____

Treatment centre: _____ Date: _____

Disease site

Pulmonary ☐ Extrapulmonary ☐ Site (specify): _____

Category of patient

New ☐ Failure ☐ Relapse ☐ TAI ☐

Transfer in ☐ Other ☐ (specify) _____

Month	Date/lab N°	Results (microscopy/culture)	Weight (kg)	Date of the next appointment
0				
2-3				
4-5				
6-8				

1. Intensive phase

Prescribed regimen and daily number of tablets

_____

_____

Month \ Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

2. Continuation phase

Prescribed regimen and daily number of tablets

_____

_____

Date / Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Remarks:

_____

_____

_____

_____

_____

10.5 - TB patient identity card

APPOINTMENT DATES

_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

IDENTITY CARD

Health unit _____

TB register N° _____

Name _____

_____

Address _____

_____

_____

_____

Sex _____

Age _____

Type of patient

New case ☐ Failure ☐

Relapse ☐ TAI ☐

Other ☐ _____

Disease classification

Pulmonary: Positive ☐ Negative ☐

Extrapulmonary: ☐ Site: _____

Date treatment started: _____

Date treatment ended: _____

Outcome (result):

Cured ☐ Failure ☐

Completed ☐ _____ ☐

REGIMEN

Initial phase

2HRZE ☐ _____

2SHRZ ☐ _____

2SHRZE/1HRZE ☐ _____

_____ ☐ _____

Continuation phase

4HR ☐ _____

6HE ☐ _____

5HRE ☐ _____

_____ ☐ _____

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In the same collection

Clinical guidelines - diagnostic and treatment manual
English, French, Spanish

Essential drugs - practical guidelines
English, French, Spanish

Obstetrics in remote settings
English, French

Management of epidemic meningococcal meningitis
English, French

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