and a high suspicion of TB disease. However, since in many countries such physicians also end up seeing cases with smear-positive results (particularly in more developed areas), these professionals must also be familiar with the recommendations and applications covered in the above section. This role of specialist physicians changes as countries develop and as TB rates are reduced, since at this point specialist physicians begin to play a more important role in case detection.

**Active detection of cases and infected individuals among at-risk populations**

Only when the first two objectives described above have been reached (i.e., the detection and cure of cases), can attempts be made to actively detect cases and infected individuals among groups at high risk of TB (i.e., sectors with disease rates of over 100 cases per 100,000 inhabitants). This can only be done in countries with good economic resources, since poor countries have many problems (ranging from economic to organisational and logistical) in implementing such a strategy. One example is limited access to tuberculin testing and the questionable validity of results, owing to the widespread practice of BCG vaccination. Active detection is most useful in individuals who have contact or live with TB cases and who have smear-positive microscopy results, and in HIV-infected subjects. It may also be useful in patients with silicosis, cases of untreated inactive TB, intravenous drug abusers, prison populations, the homeless, the poor, immigrants from high TB endemic regions, and patients with some form of immune deficiency.

However, detection of cases and infected individuals has very little epidemiological impact, since with the exception of the contacts of patients with TB disease and HIV infection, only individual benefits can be expected in the rest of the groups (because of the very limited number of cases that will be detected). Even adequate intervention among the TB contacts and HIV cases—the great majority of whom will not have TB—will have much less impact than intervention among patients. This is why such measures should not be contemplated until the primary goals of healing and case detection have been satisfied.

In this section, particularly with regards to the active detection of cases among immunocompromised patients, specialist physicians will indeed play a very important role. Management of TB contacts should preferably be done by the NTPs.
Chemoprophylaxis and BCG vaccination

In relation to the active detection of cases and infected individuals, it must be stressed that it is not only essential to treat patients, but also to provide chemoprophylaxis for infected subjects at high risk of developing active TB and to implement a system to ensure compliance. Here, it is even more difficult to ensure patient adherence when chemoprophylaxis is provided (since treatment is being administered to individuals who are not clinically ill) than when diseased patients are treated. This should not lead to a loss of prioritisation regarding the use of resources, which should always centre on treatment. Such chemoprophylaxis, which will be extensively addressed in Chapter 13, is currently referred to as the treatment of latent tuberculous infection by the American Thoracic Society and the Centers for Disease Control and Prevention. In Chapter 13, it will be pointed out that the operative efficacy of chemoprophylaxis, under NTP conditions, will depend largely on three variables: 1) the efficacy of the treatment regimen chosen; 2) the risk population designated for intervention; and 3) patient adherence to therapy. In any case, the epidemiological impact of this strategy (even when chemoprophylaxis is correctly executed) is limited, since only some potential infectious sources will be avoided, which is in contrast to treatment of diseased patients, which effectively eliminates the infectious sources of TB.

Chapter 13 will also address the subject of BCG vaccination and the fact that while studies of the efficacy of the vaccine have yielded contradictory results (good protection vs. poor or non-existent protection), the standard use of the technique is advised in newborn infants in countries with high or moderate TB endemic rates. The epidemiological impact of extensive BCG vaccination in the community has been shown to be practically zero, although it does reduce the appearance of serious TB presentations in childhood, with a resulting reduction in childhood mortality in countries where the risk of infection remains high. It is due to these individual benefits (not to the epidemiological impact) that BCG vaccination is advised.

The role of specialist physicians in this area is very limited, since such intervention should be based on the central and peripheral actions of the NTP.

Other measures

Other complementary measures can also be adopted in industrialised countries, such as the control of immigrants from highly endemic regions, the
homeless, and regional population groups in which the incidence of TB is high.

Immigrants should be subjected to control measures upon entering the country. In countries with the best antituberculous efforts, such immigrants are not granted a residency permit unless a TB study has been performed, including radiographs and tuberculin testing. Still, the great majority of immigrants do not have TB on reaching their country of destination, but instead develop the disease years later as a result of poor living conditions.

In the case of the homeless, a social service programme may be developed to allow admission to supervised residencies for the completion of therapy, or at least to provide access to hospital centres with free medication and the provision of certain incentives, such as meals.

**Measures for controlling tuberculosis transmission and their importance in the fight against the disease**

<table>
<thead>
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<th><strong>Section summary</strong></th>
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| The control of *M. tuberculosis* transmission is of extreme importance for controlling TB. However, it is necessary to evaluate the cost and benefits associated with specific measures for achieving this goal. Early diagnosis and cure is clearly the priority concern, since only in this way can infectious sources be eliminated. In comparison with these measures, the rest of interventions are very secondary and could be summarised as follows:
| – The best way to avoid the nosocomial transmission of TB is to avoid the need for patient hospitalisation.
| – Despite the acknowledged usefulness of ensuring fresh environmental air and ultraviolet (UV) radiation, in countries with low- or middle-income levels, good room ventilation would only be indicated in those areas where TB patients are found, allowing the air to circulate freely, and with natural, solar UV exposure.
| – Masks and oral protectors are most effective when used by the patient, since they prevent transmission of the aerosol form of particles that is loaded with bacilli.
| – Chemoprophylaxis and BCG vaccination have very little impact on transmission, since they do not act on the sources of infection. |

As was explained in Chapter 4, the most important mechanism for the transmission of TB which is responsible for almost all cases of infection is the airborne route. There are a series of conditioning factors that may clearly influence easier or more difficult disease transmission in the community
(e.g., degree of spread of the disease, the severity and frequency of coughing, chemotherapy, the characteristics of exposure). The control of *M. tuberculosis* transmission may thus be of extreme importance for controlling the disease. However, it is necessary to evaluate the cost and benefits associated with the use of specific measures to achieve this goal. An analysis will be made below of the potential benefits and costs of such measures.

**Early diagnosis and cure of tuberculosis cases**

Early diagnosis and cure is undoubtedly the priority concern for controlling the transmission of *M. tuberculosis*, and has been covered at length in other parts of this Guide. Nevertheless, emphasis should be placed on the fact that only correct treatment and cure of patients can help to shorten the epidemiological chain of transmission of TB to others. Only with successful treatment can the sources of infection be eliminated from the community. Hence, it is important to detect possible infectious sources as quickly as possible, particularly those individuals with smear-positive results (who are the most infectious subjects), providing them with adequate treatment. In addition, patient follow-up throughout the duration of treatment until cure is achieved is essential, as is the adoption of measures to reduce the delay in diagnosis. Apart from these measures relating to early diagnosis and cure, the remaining interventions discussed below are of secondary importance.

**Patient hospital admission**

Hospital admission plays practically no role in the control of TB. On the contrary, the best way to prevent the nosocomial transmission of TB is to avoid the need for hospitalisation. Unfortunately, it is very common in all countries (regardless of income level) to hospitalise TB patients, even though the disease will heal equally well in an ambulatory or outpatient setting. Patients should stay at home, reporting to the hospital only to receive treatment and undergo periodic control follow-ups. When the patient is diagnosed, he or she has already been transmitting the disease for a number of weeks. Furthermore, from the first day of chemotherapy, this capacity for transmission is already reduced. Hence, the patient receiving treatment on an outpatient basis will not increase the possibility of infecting those living with him or her, since it can be safely assumed that all possible cases of transmission already occurred before the diagnosis was established. What must be avoided, however, is transferring this transmission potential to other
environments and settings where the patient has not been before—which would be the case in the event of hospitalisation.

Hospital admission of a TB patient would only be warranted when the clinical situation is deemed to be extremely serious (see Chapter 9), for social reasons (e.g., extreme distance between the home and centre), or because of other suspected diagnoses.

**Room airflow renewal. Ultraviolet radiation**

*M. tuberculosis* is highly sensitive to heat, sunlight, and UV radiation. In closed rooms where none of these elements are found, the bacterium can persist with infective potential for prolonged periods of time. One of the measures that may be adopted to control TB transmission is to keep environmental air fresh and to allow exposure to UV light.

In countries with low- or middle-income levels where the ideal objectives of TB detection and cure have not yet been reached, the sole indication would be to provide good room ventilation in areas where TB patients are hospitalised, allowing the air to circulate freely, and with exposure to natural UV light. Since many of these poorer countries are located in tropical or subtropical zones, room ventilation may be allowed for several hours a day, all year round. No further resources should be spent on ventilation and UV radiation, since all efforts must focus on diagnosis and treatment.

In industrialised countries, and provided there are adequate economic resources and levels in antituberculous management, other measures can be adopted to keep environmental air fresh and to provide exposure to UV radiation. Air renewal can be achieved with machines (which vary in size, function, and price) that generate negative pressure, thereby continuously renewing the air in the room or ward. UV lamps can also be installed; this measure is much less expensive than the former, but has a similar effect to that of renewing room air several times every hour. UV radiation may therefore be regarded as more effective than air renewal. The more developed countries, which have achieved high cure rates with early diagnosis of the affected cases, should assess the convenience of having these systems (environmental air renewal and UV light) in all rooms where patients with possible TB are being studied or treated, as well as in the emergency department wards where such patients may be admitted, and in the aerosol generator systems used for induced sputum. These practices are being adopted in the great majority of hospitals in the industrialised world, although their use is suboptimal in many instances.
Masks and oral protectors

Although there has been considerable controversy regarding the true benefits of these measures, their efficacy has been acknowledged for a long time. Nevertheless, several limitations should be mentioned. The efficacy of masks used in daily clinical practice is questionable, since over 50% of the potential mycobacteria present in the environment can permeate these barriers. For this reason, such masks are most effective when worn by the patient, since they prevent the formation of bacteria-laden aerosol droplets. This same function can be achieved with handkerchiefs or oral protectors. The adoption of such measures by people living with or visiting the patient is of very limited value, even though the typical situation in hospitals corresponds to one of visitors wearing masks and the patients wearing none. The fact is that once the patient has produced these aerosol particles by coughing, others can inhale these droplets despite the wearing of masks. Hence, all patients in the contagious phases of TB (smear-positive microscopy results) should always wear masks or oral protectors.

If a mask is to be used by contacts or visitors, it must be effective in blocking the aerosol particles emitted by the affected patient. Such masks are much more expensive than the masks traditionally used in hospitals, but they are able to filter 99% of all bacilli. The best models cost more than US$10; as such, general use in a hospital would constitute a considerable expense. Such measures are thus restricted to richer countries, and only once the priority concerns of case detection and healing have been satisfied. In low- and middle-income countries, only the patient should wear a mask or oral protector.

Chemoprophylaxis and BCG vaccination

Chemoprophylaxis with isoniazid has clearly been demonstrated to be effective in people infected with \textit{M. tuberculosis} and in patients from certain TB risk groups. Chemoprophylaxis prevents infected patients from developing the disease, thus controlling transmission by preventing the appearance of infection sources in the community. However, as has been pointed out, its efficacy in controlling transmission is still far inferior to that of case detection and cure, since the latter measures act on the true sources of infection rather than on possible sources, as in the case of chemoprophylaxis.

On the other hand, although the efficacy of BCG vaccination has been contested, its use seems to be accepted in certain settings, such as in children of contagious patients who exhibit poor treatment compliance, and in health
care personnel (with negative tuberculin test readings) who are in continuous contact with TB patients. Because of the possibility that some cases of TB can be avoided with BCG vaccination, these measures could also be considered for transmission control, although the corresponding cost-efficacy ratio is very high compared with the above-mentioned alternatives. Still, it should be noted that such recommendations are not supported by scientific studies, hence the controversy and continued discussion surrounding the role of BCG vaccination.

**Recommended reading for the chapter**

Chapter 13 - Prevention of tuberculosis

Chapter summary
The best way to prevent tuberculosis (TB) is by providing appropriate treatment and curing all infectious cases. Unless high cure rates are achieved, no resources should be invested in the two other major areas of TB prevention: chemoprophylaxis and bacille Calmette-Guérin (BCG) vaccination. These two measures have very little epidemiological impact, since they do not act directly on the sources of infection. In any event, if a community has attained high cure rates, then the next focus should be on the endogenous reservoir, i.e., by offering chemoprophylaxis to infected persons who are at risk of developing TB. The BCG vaccination, on the other hand, with its zero impact on prevalence trends in the community, is recommended for reducing childhood mortality from TB.

Treatment and cure of cases
Although chapters on tuberculosis (TB) prevention traditionally include chemoprophylaxis and bacille Calmette-Guérin (BCG) vaccination, the best way of preventing TB is still by curing infectious cases, as stated previously in this Guide. As explained in Chapter 12, the most effective means of breaking the transmission chain, and thus preventing infection and possible disease in the rest of the community, is to provide appropriate treatment to cure existing cases. The treatment of TB has been reviewed at length in Chapter 9, and aspects related to the importance of healing have been covered in Chapter 12. For this reason, the importance of appropriate treatment and healing of cases will not be covered in this chapter, although it is necessary to reiterate that if these measures are not implemented correctly, there is no justification for investing any resources whatsoever in chemoprophylaxis or BCG vaccination. These last two forms of intervention, which have been the subject of much debate in the twentieth century, have scarcely had any epidemiological impact, even when implemented under the best possible conditions. Many countries have invested much money in these two measures, without even achieving minimum levels of case healing.

In any event, if a community overcomes problems of chemotherapy and achieves high cure rates, its focus should shift to the endogenous reservoir, which means offering chemoprophylaxis to infected persons at risk of developing TB. The BCG vaccination, on the other hand, with its zero impact on
endemic trends in the community, is recommended under other circumstances, such as reducing childhood mortality from TB.

**Chemoprophylaxis or treatment of latent tuberculous infection**

**Section summary**

Despite the unanimous agreement regarding indications for the treatment of latent tuberculous infection (LTBI) in certain patient groups, there is still a great discrepancy between the United States and Europe concerning recommendations for other groups of patients.

In every case of individualised indication for LTBI, the benefits and risks of employing this treatment in a person without active tuberculous disease should be carefully weighed. There are only three groups in which the indication of treatment of LTBI is unquestionable: 1) persons co-infected with *M. tuberculosis* and HIV; 2) new cases of infection, particularly in children; and 3) patients with radiological lesions suggestive of residual TB. In all other risk groups, the indication is a matter of debate and is ultimately a decision that must be made by the treating physician.

When treatment of LTBI is approached as an intervention strategy in the community, it is necessary to evaluate the operational efficiency of the measure, which will depend on three major factors: 1) efficacy of the treatment regimen used (the best is achieved with 9 months of isoniazid); 2) risk of developing TB in the group in question (only justified in HIV co-infection, new infection, and residual TB); and 3) adherence to lengthy treatment, which requires much work in order for this measure to have a successful outcome.

A National Tuberculosis Control Programme (NTP) should not spend any resources on LTBI if not enough efforts have been spent on achieving high cure rates and detection of cases. Depending on the level of treatment success and detection, extent of prevalence of the disease, and available resources and infrastructure, treatment of LTBI should be indicated as follows—in low-income countries, it should only be indicated (without effecting a tuberculin test) in HIV-infected persons and in children under the age of 5 years who have been in contact with smear-positive cases; in middle-income countries, selective LTBI treatment may be considered in specific patients (e.g., those with HIV) and large-scale LTBI treatment could be administered in children who have been in contact with smear-positive cases (without effecting a tuberculin test), with the possibility of extending the age criterion up to 10 to 15 years; finally, in developed countries, treatment of LTBI is an important strategy in dealing with the endogenous reservoir for TB disease.
Epidemiological observations during the pre-chemotherapy era of TB demonstrated that for persons who lived with infected patients, the greatest risk of developing the disease occurred during the initial weeks and months following infection, and that this risk clearly fell during the course of time. With the discovery of drugs that were shown to be effective in TB treatment, the aforementioned studies gave grounds to suggest that it was possible that if these drugs were used in this contact group, the risk could be reduced. Therefore, since the 1950s, attempts were made to reduce the disease rate in this recently infected group of persons, by administrating drug therapy despite good health. This type of therapy was referred to as preventive treatment or chemoprophylaxis. Recently, this term was changed to treatment of latent tuberculous infection (LTBI). Although the efficacy of this measure has been demonstrated in specific population groups, it has not been shown in other groups; hence, there is controversy regarding many of the indications for treatment of LTBI.

Controversy over the indications for treatment of LTBI

Among the first studies on this subject, the study by Ferebee in 1970 is of particular interest, since it not only demonstrated the increased risk among household contacts of TB patients in the initial weeks and months following the infection, but it also showed that if this contact group was administrated a long course of isoniazid, this increased risk of developing TB almost disappeared and became similar to the risk among those who had been infected more than 5 years ago. This study, together with studies of a similar group involving Eskimos, provide the best examples of the excellent efficacy of treatment of LTBI, demonstrating that it can also be highly effective if appropriately implemented as an intervention strategy in the community.

Subsequent research has since showed a notable reduction in the risk of infected persons developing the disease if they undergo treatment of LTBI. However, there are major differing opinions regarding the benefit of this form of intervention in certain risk groups. Guidelines from the United States—specifically that of the Centers for Disease Control and Prevention (CDC) and the American Thoracic Society—assert that treatment of LTBI plays a significant role in TB control; thus, they recommend a very broad use of this measure, including in almost all persons at risk of developing TB and (in the recent 2000 recommendations) even in the healthy population of a certain age. On the other hand, European societies believe that the measure should not be used indiscriminately, as they consider that treatment of LTBI
has very limited impact in TB control. The TB Working Group of the European Respiratory Society believes that treatment of LTBI should be limited to recent converters; those with untreated, inactive, or residual TB; and HIV-infected patients. The British Thoracic Society recommends limiting indications to contacts under the age of 16 years who have not received the BCG vaccination, recent converters, and immigrants.

From an objective standpoint, the impact of treatment of LTBI, implemented under NTP guidelines, should be greater in countries with low TB transmission rates (i.e., which have decades of good cure rates) and in countries where it can be presumed that the majority of new cases arise from endogenous reactivations.

In any event, there is great controversy over the subject of treatment of LTBI, when in fact, too much has been written in comparison with the number of well-designed efficacy studies that have been conducted. This may be the result of not considering when treatment of LTBI is recommended in a specific, individual case, versus when it is used in certain risk groups, as an intervention strategy that forms part of NTP actions. It is thus important to analyse the significant differences that arise from the evaluation of LTBI treatment from these two points of view.

### Rationale for recommending treatment of LTBI

It is essential to assess treatment of LTBI from two very different points of view: when it is indicated in a specific patient to obtain individual benefit, and when recommendations are for general application, for example, as an intervention strategy in certain groups in the community.

#### LTBI treatment as an individualised clinical intervention

Risk factors for developing tuberculosis

From this point of view, it is necessary to thoroughly evaluate the individual benefits and risks of LTBI treatment in a healthy subject. The three minimum requirements provided in Table 15 should be fulfilled. In practice, this implies weighing the benefits of this intervention between patients with TB infection who are at the highest risk of developing active TB (e.g., recent infection; children under 5 years; HIV infection; untreated, inactive, or residual TB) and factors that increase the risk of pharmacological toxicity (e.g., patients over the age of 35 years, alcohol intake, other diseases).
**Table 15.** Minimum requirements that should be met in order to consider the individualised clinical indication for treatment of LTBI

1. Demonstrate that the person who is to be given LTBI treatment belongs to a group that is at an increased risk of progressing to TB disease.
2. Possess evidence that intervention in this group (receiving LTBI treatment) clearly reduces the risk of developing TB disease.
3. Demonstrate that the benefit of reducing the risk of progressing to TB disease outweighs the risk of pharmacological toxicity.

In the individualised clinical evaluation, there are only three groups of subjects in whom there are reliable data from studies demonstrating (Table 15) that the indication for LTBI treatment should be conclusive (Table 16), since in these subjects the benefits (reduced probability of progressing to TB disease) clearly outweigh the possible risks. These groups are patients with *M. tuberculosis* and HIV co-infection; those with recent infection, particularly children; and those with radiological lesions suggestive of residual TB. Furthermore, in most studies of treatment of LTBI involving the three patient groups described above, it has been shown that there is low toxicity associated with the pharmacological regimen administered, which is why the balance between benefits and risks clearly tips in favour of treatment. However, except in cases of HIV infection, in the other two groups the intervention occurs in a healthy population and it is therefore reasonable to expect minimal pharmacological toxicity levels.

**Table 16.** Unquestionable indications for treatment of LTBI

1. *M. tuberculosis* and HIV co-infection.
2. Recent infection (tuberculin test converters), particularly in children.
3. Individuals with radiological lesions suggestive of untreated residual TB.

In the rest of the groups at risk of developing TB (Chapter 4, Table 1), the risk is variable, and many of these patients will experience increased pharmacological toxicity (with other underlying diseases). In the great majority of these groups, there have not yet been studies demonstrating the efficacy of treatment of LTBI. Below is a critical review of the scientific evidence available on the different risk groups and the role of treatment of LTBI as an intervention.

Co-infection with *M. tuberculosis* and HIV

The risk group that has lately been the subject of the greatest number of studies concerning treatment of LTBI is patients with co-infection with HIV
and *M. tuberculosis*, perhaps because in this group of patients it is not necessary to monitor the treatment for long periods of time in order to demonstrate treatment efficacy, unlike in other more immunocompetent groups. Most of these studies have demonstrated the efficacy of different treatment regimens used, with varying degrees of protection, depending on the treatment regimen, length, and place where the study was undertaken. Some of the studies have even shown different degrees of protection with other shorter alternative regimens that do not include isoniazid. Therefore, it has not only been demonstrated that this group of patients is at a greater risk of developing TB, but there are also sufficient studies to prove that treatment of LTBI is highly effective in these patients.

Individuals living with tuberculosis patients and recently infected persons

Most studies that were initially developed during the 1950s and 1970s with the objective of demonstrating the efficacy of treatment of LTBI included household contacts of TB patients and recently infected persons, the majority of whom had also been from the “household contact” group. These studies demonstrated a significant degree of protection in groups treated with isoniazid, and that the effectiveness of this intervention varied according to the length of treatment and the total quantity of drug taken. This is another group that has been shown to be at risk of developing TB and in which the indication of treatment of LTBI is unquestionable.

Inactive residual tuberculosis not previously treated

One of the best prospective studies that has been designed with the objective of demonstrating the utility of treatment of LTBI was the one performed by the International Union Against Tuberculosis and Lung Disease (IUATLD), which involved 27,830 healthy persons with residual TB. This excellent work (in which many other conclusions can be deduced and which will be analysed later), together with its subsequent study, clearly demonstrated the efficacy of isoniazid intervention in these subjects. This is the last group in which there is evidence showing that these persons are at a high risk of developing TB disease and that treatment of LTBI is beneficial.

Silicosis

With regards to the remaining groups at risk of developing TB disease (Chapter 4, Table 1), the only one in which studies have been effected with the objective of demonstrating the efficacy of treatment of LTBI is the group
involving patients with silicosis. Although there are studies that clearly show that this disease increases the risk of developing TB disease, only two well-conducted studies have been performed with the objective of assessing the efficacy of treatment of LTBI in these patients. While one of the studies found no evidence of protection with isoniazid + rifampicin + pyrazinamide for 3 months, the other only showed slight efficacy with the different treatment regimens studied for this intervention. Although the adverse effects did not increase, there was insufficient evidence to recommend treatment of LTBI in patients with silicosis, also especially since the risk of developing TB disease in these patients depends on the stage of the disease (silicosis stage) and the effects it has caused. For this reason, subgroups would have to be defined within this general group of silicosis patients for whom treatment of LTBI would be more justified. This, together with the fact that data from clinical studies are lacking, obscures the applicability of this intervention in this group of patients.

Prolonged corticotherapy

Patients who receive more than 15 mg of prednisolone for longer than 1 month are defined in recent CDC and American Thoracic Society recommendations as belonging to a high-risk group (where a positive tuberculin test is established at 5 mm), and treatment of LTBI is recommended in all such patients. Experimental studies have demonstrated that treatment with high-dose corticoids reduces natural resistance against *M. tuberculosis* in animals; however, the great majority of studies and articles state that this risk is minimal or almost non-existent. There are no studies demonstrating that LTBI treatment in this group reduces the risk of TB, and its possible toxicity has not been evaluated. In short, there is not enough evidence to definitively include corticotherapy amongst the groups at risk of developing TB disease, and even less evidence to justify the use of treatment of LTBI.

Diabetes mellitus

Another important risk group is patients with diabetes, because of the prevalence of the disease in the community. Although diabetic patients have for a long time been recognised as an at-risk group, there have been very few studies conducted that comprised sufficiently large patient samples. The risk of TB has been reported to be three to four times greater in diabetic patients than in healthy subjects, but the studies reporting these rates did not compare the prevalence of the infection in the community. This limitation does not
render the results totally invalid; in fact, there are other studies that do not demonstrate an increased risk, whereas there have been no studies evaluating the efficacy or toxicity of LTBI treatment in this group of patients. This paucity of data, together with the relatively low risk of developing TB disease in diabetic patients, do not justify the treatment of LTBI in these patients.

Other groups at risk of developing tuberculosis

Treatment of LTBI in the remaining groups at increased risk of developing TB disease (Chapter 4, Table 1) is also highly questionable. In many instances, the classification of some groups as “at risk” was based on the results of a very small number of studies, many of which reported very low numbers of patients who progressed to TB disease. This is the case, for example, with intravenous drug users with HIV (−); persons suffering from malnutrition; those with chronic renal failure (undergoing haemodialysis) or head and neck carcinoma; or persons who have undergone gastrectomy, jejunocolic bypass, or organ transplantation. All these groups are included in the at-risk group of subjects in whom treatment of LTBI is recommended by the American Thoracic Society and CDC in their guidelines published in April 2000.

What is irrefutable is that there are no studies that demonstrate that treatment of LTBI offers any protection against TB in these possible risk groups, or that assess the possibility of increased toxicity.

_Treatment of LTBI as an intervention strategy in the context of an NTP_

Factors determining its efficacy

A completely different approach must be adopted if treatment of LTBI is to be implemented as an intervention strategy in the community. It will be necessary to evaluate the benefits for the community under NTP conditions if this measure is implemented in selected groups, and to estimate the associated cost. Cost does not only include the price of the drugs, but also the costs associated with maintaining a health care infrastructure, which will guarantee the application of the treatment regimen, and with setting up a training programme and educational campaign, which is essential if this therapy is to be implemented correctly. The evaluation of benefits to the community will be more complex, as it will depend on the number of infected persons who will have to be given treatment of LTBI in order to prevent one case of potentially infectious TB. In the end, the operational efficiency
of administering treatment will depend on three major factors (Table 17): 1) the risk of developing TB disease in the group in question; 2) the pharmacological efficacy of the regimen employed; and 3) adherence to the prolonged treatment of LTBI.

Table 17. Factors that condition the operational efficiency of administering treatment for LTBI under NTP conditions

1. Risk of developing TB disease in the intervention group.
2. Pharmacological efficacy of the therapeutic regimen employed.
3. Patient adherence to the prolonged treatment of LTBI.

Depending on these three factors, the operational effectiveness of treatment of LTBI will vary greatly (Table 18), and its use will be fully justified in some groups but not in others. Therefore, if the risk of progressing to TB disease in the infected group is low (5%) and a low adherence rate (30%) to treatment of LTBI is also expected, even if the efficacy of the pharmacological regimen is high (80%), the operational effectiveness will be low.

Table 18. Operational efficiency of administering treatment for LTBI under NTP conditions. Number of LTBI treatments to be administered in order to prevent one case of TB

<table>
<thead>
<tr>
<th>TB risk (%)</th>
<th>Efficacy of regimen (%)</th>
<th>Adherence (%)</th>
<th>Global efficiency (%)</th>
<th>Prevention of one case</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>80</td>
<td>30</td>
<td>1</td>
<td>100</td>
</tr>
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<td>10</td>
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<tr>
<td>30</td>
<td>90</td>
<td>70</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>

* Estimated risk of developing TB disease in the group in which treatment of LTBI will be used.
† Assumed efficacy of the pharmacological regimen to be used for treatment of LTBI.
‡ Estimated percentage of LTBI treatment candidates who will complete the therapy.
§ Number of LTBI treatments to be administered in order to prevent one case of TB.

Therefore, to prevent one case of TB, it will be necessary to treat a large number of infected persons (over 100) in this risk group. This could be the case with the majority of groups that were defined earlier as having a “lower risk” of developing TB. At the other end of the scale are the groups at high risk of developing TB disease (30%), in whom if a better adherence rate is attained (50%), and there is the same treatment efficacy (80%), then opera-
tional efficiency increases and treatment of LTBI will only have to be administered to very few infected persons (less than 10) in order to prevent one TB case. These types of patients comprise the groups in which the indication for treatment of LTBI should be unquestionable, such as patients with HIV and *M. tuberculosis* co-infection, recent infection (tuberculin test converters), or previously untreated residual TB. Although the greatest risk of TB corresponds to the first of these groups (HIV infection), from a community perspective the largest number of cases can be prevented by managing the recent infection group (contacts). Thus, as an intervention strategy, treatment of LTBI in an NTP should be carried out in this group. The management of patients with HIV and *M. tuberculosis* co-infection or residual TB is more a matter of individualised clinical management, since they have less epidemiological impact than do TB contacts and those living with TB patients. The great majority of recent infections are from this latter group.

A thorough analysis will now be made of the factors that influence the operational efficiency of implementing LTBI treatment under programme conditions.

Efficacy of LTBI treatment as a conditioning factor for operational efficiency

Of the three factors that influence the operational efficiency of LTBI treatment, the one regarding the efficacy of the pharmacological regimen used will be a consistently critical factor. Until the onset of the HIV epidemic, most studies on LTBI treatment only included the use of isoniazid for different treatment lengths. However, in recent years, research on patients with HIV and *M. tuberculosis* co-infection has demonstrated that other drug regimens can be equally effective, with the important advantage that treatment time can be reduced, which helps to improve patient adherence. It has yet to be demonstrated, however, that these regimens are also effective in immuno-competent persons. It should not be forgotten than in subjects with relatively healthy immune systems, *M. tuberculosis* is usually in a latent state or has little metabolic activity, and under these circumstances these subjects will not be susceptible to antibiotic action. This explains why the best efficacy is observed with the longer regimens for isoniazid. It is likely that these circumstances also apply to other drugs, such as rifampicin and pyrazinamide (despite their greater sterilizing action), although it is yet to be demonstrated whether 2- or 3-month regimens with these drugs are effective in immuno-competent persons (i.e., in household contacts of TB patients and healthy converters), or in other subjects in whom immunodeficiency is not as serious.
a problem as for HIV-infected persons. In HIV-infected patients, shorter regimens may be more appropriate because, considering the severe immunodeficiency, it can be assumed that the bacilli will have higher metabolic activity (thus facilitating antibiotic action, even over short periods), and a smaller proportion of bacilli will be found in a latent state. In any event, in consideration of the above and the high hepatic toxicity that has been demonstrated with the combination of rifampicin and pyrazinamide, this regimen cannot be recommended for routine use.

With regards to isoniazid, there has been much debate concerning the optimal length of time for treatment of LTBI in order to achieve maximum efficacy. Data from three major studies—the Ferebee study involving contacts, the Comstock studies on Eskimos, and the IUATLD multicentre study on residual TB—suggest that the best protection is perhaps provided with 9 to 10 months of isoniazid. Based on available data to date, LTBI treatment is most efficacious in the form of 9 months of isoniazid. The dose of isoniazid is the same as in treatment: 5 mg/kg body weight per day for adults and 10 mg/kg body weight per day for children, not to exceed 300 mg/day in either case (Chapter 9).

The risk of developing tuberculosis disease as a conditioning factor for LTBI treatment operational efficiency

Another factor influencing the operational efficiency of LTBI treatment is the risk of developing TB disease among different groups. As illustrated in Chapter 4 (Table 1), this risk can be estimated and used to define very high-risk groups in which intervention should be implemented automatically (Table 16), and to define lower-risk groups in which LTBI treatment is the subject of great debate and thus would be difficult to recommend in a control programme.

Of the three aforementioned groups in which intervention is unquestionable (Table 16), the most important group from an NTP management perspective pertains to persons living with TB cases and recent converters. The operational efficiency of LTBI treatment in this group will be influenced by the age of the contact person and the prevalence of the infection in the different age groups. For example, a child contact aged 5 to 10 years in a developed country where the prevalence of infection is less than 1% for this age group will not be managed in the same way as a 50-year old adult in a poor country with infection prevalence rates of over 75%. In the first case, the infected subject is almost always a recent converter and the efficacy of LTBI treatment is unquestionable. In the second case, however, it is highly likely
that the infection has occurred before the present contact, and therefore LTBI treatment efficacy will be practically zero. This is why, depending on the prevalence of infection in the different age groups, an evaluation should be made of the age below which treatment of LTBI should be recommended to contacts. This issue has hardly been discussed by scientific societies.

Adherence to LTBI treatment as a conditioning factor for operational efficiency

This third factor is where most work can be done by an NTP. If treatment abandonment among TB patients is the biggest obstacle encountered by NTPs, it should be remembered that this rate would increase in infected subjects, because LTBI treatment in a healthy population has to be maintained for longer than for those with TB disease. Many studies have demonstrated minimum adherence to this treatment, although some studies have shown that adherence in itself is not as important as the fact that the patient must take the recommended number of tablets, albeit over a longer period. For this reason, the training and education of health personnel, together with other important measures, are fundamental if treatment of LTBI is to be used as a strategy by the NTP. Some programmes in places such as Cuba and New York have introduced directly observed LTBI treatment, albeit on different scales, which has been shown to improve patient compliance and increase the operational efficiency of this intervention. However, cost-efficacy studies are still needed to assess the public health value of this strategy. It is likely that too high an investment is required in comparison with the achievements that are obtained from a community perspective.

Other factors conditioning treatment of LTBI operational efficiency

Other factors, such as the characteristics of the health system and the individual being treated, are also important and may determine if LTBI treatment is suitable, particularly since such factors play a role in an early diagnosis of TB in the event that the disease develops. It is also important to consider the risk level of those who live with TB cases and of the community that is in contact with the possible future TB case (if LTBI treatment is not be administered). In short, it will be necessary to analyse the characteristics and circumstances of the susceptible individuals described above, since contacts such as children in nurseries, prison inmates, and elderly residents in nursing homes differ from adults without risk factors. This difference in community risk is that which persuaded the CDC and the American Thoracic Society to include the first group of contacts in their LTBI treatment recommendations.
Finally, another important factor is the necessity to demonstrate that the individual who is under consideration for LTBI treatment is infected by *M. tuberculosis*. It is well known that the only available method for demonstrating this infection is the tuberculin test, which is associated with significant limitations, particularly with regards to preservation of the tuberculin, application and reading of the test, false positives and false negatives, and the window period between onset of infection and positivity of the purified protein derivative in recently infected patients and contacts. This subject has been reviewed at length in Chapter 6 of this Guide and should be given careful consideration when deciding on an intervention in the community. As it can be seen, the community perspective on treatment of LTBI as an intervention depends on a large number of complex factors that vary by country, region in the country, the achievements and motivation of the local NTP, and, above all, the risk of developing TB disease. Resources should only be spent on the management of contacts, those who live with TB patients, and recent converters.

**Importance of LTBI treatment in NTP strategies**

When LTBI treatment is analysed as an intervention strategy, under no circumstances can it be compared with appropriate chemotherapy and curing of TB cases. It must be remembered that there is almost 100% efficacy in correct TB treatment, and that its operational efficiency is much higher, particularly because this measure eliminates sources of infection, whereas LTBI treatment only prevents infection in certain cases. Therefore, when TB treatment is implemented appropriately, not only does the patient benefit (as in cure and prevention of possible death), but so does the entire community, since the source of infection is eliminated. In contrast, this benefit is highly uncertain with LTBI treatment. This is why a TB control programme should not waste any of its resources on treatment of LTBI without previously having worked actively on case detection and having attained high cure rates of above 85% to 90%. There are many areas in the world, particularly in medium- and high-income countries, where LTBI treatment has been adopted as a strategy in the last few decades, but where there is often little enthusiasm to achieve high cure rates.

If we divide the world according to the epidemiology of TB, available resources, and the appropriateness of anti-TB campaigns carried out in the past, we can clearly identify three major blocks:
– The first block consists of low-income countries, where the disease is highly prevalent and there has been little use of appropriate TB control measures. There is no doubt that in this group of countries, which includes most countries in Africa and Asia and certain zones of Latin America (accounting for an estimated 80% of TB burden in the world), all resources must be invested in achieving appropriate treatment and in guaranteeing a health infrastructure that permits implementation of directly observed treatment and the detection of cases through smear microscopy. Furthermore, in this block, since there is mass BCG vaccination in infants (many schoolchildren are also revaccinated), and peripheral health centres do not have the facilities to conserve tuberculin, the use of the tuberculin test to detect infected cases is not valid. Thus, extensive use of LTBI treatment should only be indicated (without having to perform the tuberculin test) in contacts of smear-positive cases under the age of 5 years, in order to lower TB-related mortality. Cases of HIV and *M. tuberculosis* co-infection are also indicated.

– The second block comprises middle-income countries, where TB rates are high but not as high as in poorer countries, and where despite having had NTPs for many years, there has been limited impact on the decline in TB rates. In this group, which includes the large majority of Latin America and Eastern Europe, and some countries in Asia, mass BCG vaccination is widespread, and there is a lack of facilities to guarantee proper conservation of tuberculin in peripheral health centres. Still, these countries have more resources and a better health infrastructure than do the poorer countries, and their priority is to invest in case detection and attain high cure rates. Only when progress is made with respect to case detection and high cure rates should LTBI treatment be considered in specific risk groups. LTBI treatment should be offered to those patients with HIV infection and contacts of smear-positive cases (without performing tuberculin tests), with consideration of extending the age range in these contacts by up to 10 to 15 years.

– Finally, the last block comprises developed countries, which are characterised by low TB rates and good NTPs that have implemented effective TB control for many decades. Most of these countries have been attaining the priority objectives with regard to case detection and high cure rates for many years now. Furthermore, many do not vaccinate and all possess facilities to conserve tuberculin in all health centres. For these reasons, LTBI treatment is indeed an important intervention strategy in these countries when dealing with the endogenous reservoir for TB disease. Thus,
the inclusion of LTBI treatment as an intervention strategy in the NTPs of these countries should be evaluated. However, the epidemiological impact of this measure is very low, and its use implies spending large amounts of resources. A thorough evaluation must be made to select the risk groups that are to receive LTBI treatment, and to determine how such intervention should be performed, either on an individualised basis or universally to achieve a community-wide impact.

Recommended reading

BCG vaccination

Chapter summary

In 1919, after 13 years and 230 consecutive passages, Albert Calmette and Camille Guérin obtained a live *M. bovis* strain with attenuated virulence. At present, there are four varieties of these strains that are distributed by the United Nations Children’s Fund (UNICEF): French (Pasteur) 1173 P2, Danish 1331, Glaxo 1077, and Japanese 172.

Some of the most important negative aspects of this vaccine are that it interferes with the tuberculin test result, thus complicating the indication for the treatment of LTBI; it is associated with complications; and its cost-benefit ratio is uncertain. Furthermore, many aspects of the immunological response to the BCG vaccine are unknown, although it is clear that the vaccine offers limited immunity against certain *M. tuberculosis* antigens.

The best means of evaluating the efficacy of the vaccine is through controlled clinical trials and case-control studies. However, both have yielded markedly different rates of protection by the vaccine, ranging from 0% to 80%. Many factors have been proposed to explain these differences. Meta-analyses have reported high vaccination efficacy (75-86%) against TB meningitis and miliary TB, but only moderate overall efficacy (50%). There is no evidence or theoretical rationale to justify re-vaccination in schoolchildren.

The BCG vaccination does not prevent *M. tuberculosis* infection or protect previously infected cases; its protective effects are inconstant, temporary, and time limited. Perhaps its best action is the protection it offers against disseminated TB and severe forms of TB that can occur after primary infection, especially in children. Even if it is implemented under the best conditions, and presuming maximum efficacy, it has very little impact on the endemic rate and does not help to reduce the annual rate of infection.

Considering the above, wide-scale BCG vaccination at birth should be employed as an intervention strategy in all countries with high or moderate TB prevalence rates, not because of its epidemiological impact, but so as to reduce infant mortality. In countries with low TB prevalence rates, where infant mortality from TB was overcome decades ago, BCG vaccination is not indicated.

A brief history

When Robert Koch demonstrated in 1890 that TB was an infectious disease, work commenced in different parts of the world to develop a vaccine. However, the only anti-TB vaccine that has been widely used in the world is the one obtained from *M. bovis* by Albert Calmette and Camille Guérin at the Pasteur Institute in Lille. In recognition of their discovery, it became known
as the bacille Calmette-Guérin (BCG) vaccine. Calmette and Guérin believed that it was necessary to obtain live avirulent bacilli, capable of producing systemic and local immunity in the digestive tract, which at the time was considered to be the disease’s principal route of access. They commenced their studies in 1906 with a bovine bacillus strain isolated in the milk of a cow with tuberculous mastitis, and observed that consecutive passages in this culture medium progressively reduced the virulence of the bacillus. After 13 years and 230 consecutive passages, it was believed that characteristics of the bovine bacillus could no longer be modified as they were hereditarily fixed. They had obtained a new strain of bovine bacillus, which they named the bile bacillus of Calmette and Guérin, or BCG.

In 1921, the first experiments involving vaccinations in humans began, and on June 25, 1924, Albert Calmette reported the results to the Medical Academy of Paris. From then on, mass vaccination was commenced in children in France. BCG strains were distributed to different countries, which also began vaccinations. The end of the Second World War brought about mass use of BCG vaccination as a preventive measure against TB. It was initiated by the Red Cross in Denmark in 1947, and Sweden and Norway soon joined the International Tuberculosis Campaign, which grew rapidly. By 1948, approximately 5 million persons had been vaccinated in 35 countries, and BCG vaccination was considered the only method that achieved effective immunity against TB. By the 1970s, the vaccination was provided in 169 countries and an estimated 2000 million persons had received it. In 1988, the World Health Organization (WHO), as part of its Health for All in the Year 2000 Programme, included the BCG vaccination in the Expanded Programme on Immunisation.

Immunogenic differences of BCG attributable to the production process

When the use of the vaccine became widespread, the original BCG strain was distributed to different laboratories worldwide, in light of keeping the strain alive and preparing BCG vaccinations for subsequent use. In the 1950s, it was confirmed that there were marked differences in the immunogenicity of vaccines prepared by the different laboratories, since the techniques in culture maintenance and vaccine preparation had been adapted to the individual characteristics of each laboratory. Even the vaccines prepared in the same laboratory revealed significant differences. It was therefore decided that it was necessary to standardise the vaccine, taking into consideration the
purity of the strain, its viability, the pathology caused in animals, local lesions caused by vaccination in humans, tuberculin test conversion, and immunity provided in animals and humans. In 1959, a study was begun, coordinated by the WHO Research Office in Copenhagen, with the participation of laboratories from seven countries, to analyse each laboratory’s methods of evaluating the vaccine. Participating laboratories were given the same vaccines: the freeze-dried Japanese vaccine (strain 10-034 A) and the liquid Danish 1343. The findings were startling; the live unit count for the same vaccine, assessed with a strict and standardised technique, varied not only from one laboratory to another, but also within the same laboratory, with much wider margins than expected.

The use of BCG vaccination in mass worldwide campaigns revealed other problems, such as the importance of transportation and conservation of the vaccine until its use. The allergenic potency of the live BCG vaccine is reduced considerably when stored above 30ºC, even for a short period of time. In order to prevent unforeseen and undetected modifications in the biological properties of the BCG strain, it was recommended to use a seed-lot system in vaccine production. A seed-lot comprises a certain amount of BCG strain, of uniform composition, that is used as a seed in the preparation of BCG cultures. The colonies are harvested from the primary seed-lot for successive passages, up to a maximum of 12 passages. Nowadays, the preparation method has been standardised and it is always used in vaccine production.

However, although all vaccines come from the same master strain created by Calmette and Guérin, each laboratory that produces the BCG vaccine maintains the corresponding substrains by means of successive passages and different methods, which has brought about morphological, physical, and biological changes in the initial bacillus. It was suspected that these mutations were also of a genetic nature, a hypothesis that was subsequently confirmed with molecular biological techniques. This may at least explain in part the differences observed in the immunogenicity and efficacy of the different vaccines.

**Recommended vaccines and vaccination techniques**

Since 1960, the WHO has recommended that cultures be stabilised through lyophilisation and freezing in order to reduce the possible immunogenic differences observed in different vaccine strains.

At present, there are four strain varieties distributed by UNICEF:

- French (Pasteur) 1173 P2.
- Danish 1331.
– Glaxo 1077; this strain, which was obtained in Copenhagen in the 1950s and was derived from the Danish 1331 strain, is somewhat different. (Merieux in France and Evans in the United Kingdom use this strain).
– Japanese 172, selected because of its high resistance to lyophilisation and because it is more stable to heat.

In addition, there are other vaccine strains that are widely used in the world, such as Moreau (Brazil), Montreal (Canada Connaught), Russian (Russia), and Tice (United States).

A live vaccine contains approximately $10^8$ bacilli per mg of BCG, although it will only provide between $5 \times 10^6$ and $45 \times 20^6$ colony-forming units (CFU). The proportion of viable BCG bacilli may be halved after drying and freezing.

Although Calmette and Guérin commenced their studies employing the oral route for vaccination, the method of choice to perform BCG vaccination is by intradermal injection, which was recommended at the First International BCG Congress in 1948, and subsequently by the WHO Expert Committee. This route of administration was introduced in Sweden in 1928 and it is used because it permits correct dosage.

A special BCG is required for intradermal injection and it is administered at a dose of 1/20 mg of BCG diluted in 0.1 ml, although in children under 1 year, half of this amount is recommended with the same concentration. This dose is injected intradermically in the deltoid region, in order to produce an oedematous papule with a diameter of 8 to 10 mm. After 2 to 3 weeks, there will be central necrosis at the injection site, developing into a pustule or small blister that will secrete a thick serous liquid; this will resolve spontaneously in 3 to 4 weeks, leaving a scab for a further 6 to 12 weeks that will then fall off and leave a depressed, round, blanched scar.

Prior considerations and deficiencies in the BCG vaccine that may affect its indication

Before analysing the efficacy and possible indications of the BCG vaccine, it is necessary to consider a series of extremely important practical factors regarding its limitations, which may affect its indication in different regions. The most important factors are:
– BCG vaccination interferes with tuberculin test results, as explained in Chapter 6. This will hinder the interpretation of the only technique available for the diagnosis of tuberculous infection.
– It will also hinder possible indication for treatment of LTBI, a TB control strategy that, as has already been analysed, is much more effective than BCG vaccination.

– The vaccine is not harmless. There are potential complications, particularly in immunosuppressed individuals, because the vaccine involves a strain with live bacilli. This is a common source of controversy, particularly because of its wide-scale use in countries with a high prevalence of HIV.

– The cost-benefit ratio has not been sufficiently studied despite the amount of research conducted on the subject. The truth is that these efficacy studies are very difficult to perform and compare. The uncertainty about the cost-benefit ratio is one of the biggest limitations in the possible recommendation of the vaccination, and it explains, in part, the enormous differences encountered from one zone to another. This point will be discussed in further detail later in this Guide.

– The influence of the complexity of the TB immune response (covered in Chapter 5). Many aspects of the immunological response to BCG vaccination are still unknown. In any event, the BCG vaccination affords a limited immunity to certain important antigens to \( M. \) \( tuberculosis \)—e.g., secretion proteins, Ag 30-32 kD.

– The presence of cell hyperactivity (positive tuberculin reaction) is not synonymous with protection.

– There are many factors that influence the vaccine quality, such as the percentage of viable bacilli present in each vaccine dose, culture dispersion, and lyophilisation method.

– Despite the intradermal route being the recommended route of administration, other routes have also been used, such as the oral route. Of late, the inhalatory route is being tested, which would permit a specific local response.

– The fact that a third of the world population is infected makes this vaccine useless in this segment of the global population. One possibility of improving the BCG vaccine would be to develop one that destroys the bacilli inside the macrophages.

**Assessment of BCG vaccination efficacy**

Since the very beginning of the mass vaccination campaigns, it was clear that there were great differences in the protection afforded by the vaccine depending on the different regions where it was used. Protection rates were over 80% in certain areas, and yet in others vaccinated individuals were more likely to develop TB than those who were not vaccinated. From the
start, it was observed that it was very difficult to assess the efficacy of this vaccine, and comparing results was even more difficult. Attempts to assess the efficacy of the vaccine have been based on:

**BCG scar**

The presence of a vaccination scar is one of the objective indicators of vaccination. However, the size of the local reaction and the scar are related to the dose and the level of BCG bacilli (either dead or alive) in the vaccine, and to the type of vaccine used. Usually, the vaccination scar is permanent, but small scars and those that result from low vaccine doses may disappear in the course of time. The vaccination scar is not synonymous with protection, although it is believed that if no reaction or scar occurs, no type of protection is possible.

**Tuberculin testing**

Although the BCG vaccine clearly interferes with tuberculin test results, it is not known to what extent this is true. Therefore, although it is possible that in some individuals it causes significant interference for many years, in others there is hardly any interference. All this is difficult to estimate or predict. In any event, a positive tuberculin test after vaccination is not synonymous with protection, although it is reasonable to assume that if the vaccine is not even capable of converting the tuberculin test, it will not be able to offer any level of protection. The relation between skin test reaction and the BCG vaccine is closely connected to the number of viable bacilli in the vaccine (which may range from $5 \times 10^6$ to $45 \times 10^6$).

**Inoculation in animals**

The few animal studies that have attempted to quantify the efficacy of the BCG vaccine have been unsuccessful.

**Controlled clinical studies**

Almost all controlled clinical studies of BCG vaccination have significant methodological limitations, although the controlled trial is the least ambiguous method to evaluate vaccination efficiency. In this type of study, vaccinated subjects are monitored for a certain period of time, with the objective of determining the rate of onset of disease in the presence of a certain factor or exposure, which, in this case, is BCG vaccination.
The results of the major controlled clinical studies of the efficacy of BCG vaccination are highly discordant (Table 19). In a study involving Native American Indians, the vaccination efficacy observed over a 20-year period was 80%. In contrast, the vaccination efficacy among schoolchildren in Puerto Rico, after 7 years of observation, was 31%. The Medical Research Council studied intradermal vaccination in 14,100 schoolchildren aged 14 to 15 years, comparing results from this group with that from a control group of 13,200 individuals. Findings, which were published every 5 years, revealed high and consistent vaccination efficacy over the 20 years of observation (81% vs. 76%). However, in two studies conducted in India, the first study (in Madanapalle; 1950-1955) revealed a vaccination efficacy of 57%, whereas the second study (in the district of Chingleput; 1968-1971), which included 115,000 tuberculin-negative individuals over the age of 1 month, revealed very low levels of protection: 17% in children aged 0 to 14 years and 0% in those over the age of 14 years. These results were somewhat surprising as this study was one of the best-designed studies on vaccination efficacy.

Vaccination in infants at birth has also been analysed in different controlled studies, again with highly discordant results. Aronson and colleagues reported an efficacy of 59% in Indian babies vaccinated at birth. However, Sergent and colleagues observed a vaccination efficacy of 6% to 36% after 7 years among 20,174 vaccinated newborns; whereas Curtis observed a 75% vaccination efficacy rate in newborns in Manchester, England.

Table 19. Major controlled clinical studies evaluating the efficacy of BCG vaccination

<table>
<thead>
<tr>
<th>Place</th>
<th>Age at vaccination (years)</th>
<th>Vaccinated population</th>
<th>Monitoring (years)</th>
<th>Vaccination efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>0-20</td>
<td>North American Indians</td>
<td>9-11</td>
<td>82</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>1-18</td>
<td>Schoolchildren</td>
<td>18-20</td>
<td>29</td>
</tr>
<tr>
<td>Georgia</td>
<td>5-17</td>
<td>Schoolchildren</td>
<td>20</td>
<td>57</td>
</tr>
<tr>
<td>Georgia and Alabama</td>
<td>&gt; 5</td>
<td>General population</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Chicago</td>
<td>Newborn infants</td>
<td>Contacts with TB patients</td>
<td>12-24</td>
<td>75</td>
</tr>
<tr>
<td>England</td>
<td>14-15</td>
<td>Schoolchildren</td>
<td>15</td>
<td>77</td>
</tr>
<tr>
<td>France</td>
<td>6-14</td>
<td>Schoolchildren</td>
<td>20</td>
<td>74</td>
</tr>
<tr>
<td>Madanapalle (India)</td>
<td>All ages</td>
<td>Rural</td>
<td>20</td>
<td>19.5</td>
</tr>
<tr>
<td>Chingleput (India)</td>
<td>All ages</td>
<td>Rural</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>New York (US)</td>
<td>Newborn infants</td>
<td></td>
<td>2-13</td>
<td>6.6</td>
</tr>
<tr>
<td>Saskatchewan (Canada)</td>
<td>Newborn infants</td>
<td>North American Indians</td>
<td>15</td>
<td>81</td>
</tr>
</tbody>
</table>
Case-control studies

In these studies, subjects are selected precisely because of the presence (cases) or absence (controls) of disease. These studies require a strict design and appropriate statistical analysis, as they may present significant bias. Since they are retrospective studies, verification of vaccination history is a problem. Furthermore, it is not sufficient to check for the presence of a scar, which would overestimate vaccination efficacy.

Results from case-control studies of vaccination efficacy have also been highly discordant (Tables 20 and 21), with a maximum efficacy of 84% and a minimum of 0%. Differences in the methodology of these studies have been detected, which may have influenced the efficacy rates obtained. In Yaounde, Cameroon, the BCG vaccination was administered to individuals aged 0 to 18 years without previous tuberculin reaction, in a population with a 25% prevalence of tuberculous infection in this age group. TB was ruled out in the control group only on the basis of the absence of symptoms.

Table 20. Major case-control and contact studies evaluating the efficacy of BCG vaccination

<table>
<thead>
<tr>
<th>City/region (country)</th>
<th>Age at vaccination (years)</th>
<th>Age at time of study (years)</th>
<th>Clinical forms of TB observed</th>
<th>Vaccination efficacy (%) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case-control studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sao Paulo (Brazil)</td>
<td>Newborn infants</td>
<td>&lt; 5</td>
<td>Meningitis</td>
<td>87 (72-94)</td>
</tr>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>Newborn infants</td>
<td>&lt; 5</td>
<td>Meningitis</td>
<td>92 (65-98)</td>
</tr>
<tr>
<td>Study 3</td>
<td>Newborn infants</td>
<td>&lt; 5</td>
<td>Meningitis</td>
<td>29 (-120-77)</td>
</tr>
<tr>
<td>Delhi (India)</td>
<td>Newborn infants</td>
<td>&lt; 5</td>
<td>Meningitis</td>
<td>84</td>
</tr>
<tr>
<td>Bangkok (Thailand)</td>
<td>Newborn infants</td>
<td>&lt; 15</td>
<td>All</td>
<td>73 (13-94)</td>
</tr>
<tr>
<td>Madras (India)</td>
<td>Newborn infants</td>
<td>&lt; 12</td>
<td>Meningitis</td>
<td>77 (71-83)</td>
</tr>
<tr>
<td>Sao Paulo (Brazil)</td>
<td>0-1</td>
<td>&lt; 13</td>
<td>Meningitis</td>
<td>74 (41-92)</td>
</tr>
<tr>
<td>Buenos Aires (Argentina)</td>
<td>Newborn infants</td>
<td>&lt; 6</td>
<td>All</td>
<td>73 (48-83)</td>
</tr>
<tr>
<td>Manitoba (Canada)</td>
<td>Newborn infants</td>
<td>&lt; 15</td>
<td>All</td>
<td>70 (48-83)</td>
</tr>
<tr>
<td>Yaounde (Cameroon)</td>
<td>0-18</td>
<td>17-26</td>
<td>Bacill. pulm.</td>
<td>66 (53-75)</td>
</tr>
<tr>
<td>Birmingham (England)</td>
<td>3 months</td>
<td>&lt; 13</td>
<td>All</td>
<td>64 (43-72)</td>
</tr>
<tr>
<td>Nagpur (India)</td>
<td>Newborn infants</td>
<td>11-30</td>
<td>Pulmonary</td>
<td>60 (43-72)</td>
</tr>
<tr>
<td>Alberta (Canada)</td>
<td>Newborn infants</td>
<td>0-30</td>
<td>All</td>
<td>57 (23-75)</td>
</tr>
<tr>
<td>New Delhi (India)</td>
<td>Newborn infants</td>
<td>&lt; 5</td>
<td>Meningitis</td>
<td>57</td>
</tr>
<tr>
<td>London (England)</td>
<td>0-1</td>
<td>0-14</td>
<td>All</td>
<td>49 (14-70)</td>
</tr>
<tr>
<td>Cairo (Egypt)</td>
<td>0-14</td>
<td>0-14</td>
<td>Pulmonary</td>
<td>49 (25-57)</td>
</tr>
<tr>
<td>Rangoon (Burma)</td>
<td>Newborn infants</td>
<td>&lt; 5</td>
<td>All</td>
<td>38 (12-50)</td>
</tr>
<tr>
<td>Jakarta (Indonesia)</td>
<td>Newborn infants</td>
<td>&lt; 5</td>
<td>All</td>
<td>37 (3-62)</td>
</tr>
<tr>
<td>Queensland (Australia)</td>
<td>12-14</td>
<td>15-94</td>
<td>All</td>
<td>33 (-5.58)</td>
</tr>
<tr>
<td>Barcelona (Spain)</td>
<td>Newborn infants</td>
<td>4-21</td>
<td>All</td>
<td>32 (0.1-49)</td>
</tr>
<tr>
<td>Colombo (Sri Lanka)</td>
<td>Newborn infants</td>
<td>&lt; 9</td>
<td>All</td>
<td>17 (-21-48)</td>
</tr>
<tr>
<td>City/region (country)</td>
<td>Age at vaccination (years)</td>
<td>Age at time of study (years)</td>
<td>Clinical forms of TB observed</td>
<td>Vaccination efficacy (%) (range)</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------</td>
<td>----------------------------</td>
<td>------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Cali (Colombia)</td>
<td>Newborn infants</td>
<td>&lt; 15</td>
<td>All</td>
<td>16 (-62-57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15-36</td>
<td>All</td>
<td>9 (0-61)</td>
</tr>
<tr>
<td>Santiago (Chile)</td>
<td>Newborn infants</td>
<td>&lt; 6</td>
<td>All</td>
<td>2 (-82-45)</td>
</tr>
<tr>
<td></td>
<td>(revaccination at 6 and 12 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lusaka (Zambia)</td>
<td>Newborn infants</td>
<td>&lt; 6</td>
<td>All</td>
<td>0 (-360-80)</td>
</tr>
<tr>
<td></td>
<td>HIV +</td>
<td></td>
<td></td>
<td>59 (8-82)</td>
</tr>
<tr>
<td></td>
<td>HIV –</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Santa Fe (Argentina)</td>
<td>Newborn infants</td>
<td>0-14</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td>Lome (Togo)</td>
<td>Newborn infants</td>
<td>0-7</td>
<td>All</td>
<td>66 (54-74)</td>
</tr>
<tr>
<td>Bangkok (Thailand)</td>
<td>Newborn infants</td>
<td>&lt; 6</td>
<td>All</td>
<td>74 (62-82)</td>
</tr>
<tr>
<td>Seoul (Korea)</td>
<td>Newborn infants</td>
<td>6</td>
<td>All</td>
<td>71 (56-81)</td>
</tr>
<tr>
<td>Bangui (Cent. Afr. Rep.)</td>
<td>Newborn infants</td>
<td>6</td>
<td>All</td>
<td>71 (56-81)</td>
</tr>
<tr>
<td>Barcelona (Spain)</td>
<td>Newborn infants</td>
<td>&lt; 6</td>
<td>All</td>
<td>74 (62-82)</td>
</tr>
</tbody>
</table>

However, these studies demonstrated that vaccination efficacy was greater in patients with disseminated or meningeal forms of TB (Table 21), and that there was much inconsistency in the relation between vaccination efficacy and the time elapsing after vaccination.

**Table 21.** BCG vaccination efficacy (as a percentage) in the prevention of different clinical forms of tuberculosis, according to the major case-control studies

<table>
<thead>
<tr>
<th>City/region (country)</th>
<th>Meningitis</th>
<th>Miliary TB</th>
<th>Pulmonary TB</th>
<th>Pleural TB</th>
<th>All forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sao Paulo (Brazil)</td>
<td>86.8</td>
<td>92.0</td>
<td>29.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangkok (Thailand)</td>
<td>100</td>
<td>100</td>
<td>64</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Buenos Aires (Argentina)</td>
<td>100</td>
<td>78</td>
<td>64</td>
<td>57</td>
<td>96</td>
</tr>
<tr>
<td>Madras (India)</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yaounde (Cameroon)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>England</td>
<td>70</td>
<td></td>
<td>66*</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Santiago (Chile)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Rangoon (Burma)</td>
<td>52</td>
<td>80</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papua (New Guinea)</td>
<td>58</td>
<td>70</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jakarta (Indonesia)</td>
<td>75</td>
<td></td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barcelona (Spain)</td>
<td>-40†</td>
<td>12*</td>
<td>38</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

* Bacilliferous post-primary pulmonary TB.
† Extrapulmonary TB.
‡ Primary pulmonary TB.
Studies of contacts

These studies have been conducted in countries where BCG vaccination is mandatory for newborns. The effect of the vaccination was analysed in children who were studied as contacts with an index case; comparisons of results depended on whether there was a vaccination history. In these studies (the results of which are illustrated in Table 20), the vaccination efficacy rates were 66% in Lome, Togo; 53% in Bangkok, Thailand; 71% in Bangui, Central African Republic; and 74% in Seoul, Korea. Another important conclusion drawn by these studies is that the protective effects decrease in the course of time, decreasing from 79% in children under the age of 1 year to 46% in children aged 4 to 5 years in Seoul.

Meta-analysis of studies on BCG vaccination efficacy

Considering the marked differences among results of studies of the efficacy of BCG vaccination, an attempt has been made to obtain an objective interpretation of the combined results of the different studies using meta-analysis statistical techniques. Ten controlled clinical studies were analysed, obtaining statistically significant heterogeneity in vaccination efficacy ($P < 0.001$), and it was therefore considered inappropriate to calculate a global protection effect. Vaccination efficacy was high (86%) against tuberculous meningitis and miliary TB. In case-control studies, heterogeneity was also high, although less in pulmonary TB ($P < 0.02$), presenting greater homogeneity against meningitis and miliary TB with a global protection effect of 75% against these forms of the disease.

Colditz and colleagues have performed two meta-analyses. In the first, a protective effect of 51% was obtained in controlled clinical studies and 50% in case-control studies. The second study, which analysed vaccination efficacy in children, reported an average protective rate of 74% in four controlled studies and 52% in nine case-control studies. However, these studies have received much criticism because they did not adjust for possible heterogeneous factors influencing the use of the BCG vaccination in the different studies, such as differences in populations, risks of infection and/or TB disease, vaccines, and methods of case-control selection.

Factors influencing the differences in BCG vaccination efficacy

The BCG vaccine, which is employed in different parts of the world, differs considerably in biological and even genetic characteristics, as well as in other factors such as conservation method and transportation. These differ-
ences have been used to explain the discrepancy in results from the various efficacy studies. The most important factors that may cause such differences are detailed in Table 22. As can be seen, there are many factors involved, among which one of the most significant is infection by environmental mycobacteria. These mycobacteria may afford a slight degree of protection in non-vaccinated individuals, which would therefore lower vaccination efficacy. This is one of the most important factors that has been used to explain the fact that studies conducted in tropical regions, where in theory there are more environmental mycobacteria, have always reported a lower degree of protection than studies performed in non-tropical areas.

Table 22. The most significant factors that may cause the marked differences found in the efficacy of the BCG vaccine in different studies

1. Attributable to the vaccination:
   - Vaccination technique
   - Dose administered
   - Vaccination age
2. Attributable to the vaccine:
   - Transportation
   - Conservation
   - Viability of the vaccine
   - Different classes of vaccine used
   - Different culture methods employed in its preparation
3. Variables that may influence the host-vaccine interaction:
   - HIV infection
   - Immunosuppression
   - Severe malnutrition
   - Others
4. Previous infection from environmental mycobacteria
5. Methodological differences in the planning and development of studies
6. Possibility of reinfection by highly virulent strains of *M. tuberculosis* in individuals protected by the BCG vaccine
7. Differences amongst individuals in different populations

Conclusions on BCG vaccination efficacy

In conclusion, it is perhaps possible to summarise the following about the BCG vaccine:
- It does not prevent *M. tuberculosis* infection.
- It does not protect individuals with previous infection.
- It affords inconstant, temporary, and time-limited protection.
- It hinders the predictive value of the tuberculin test, and therefore interferes in the appropriate implementation of LTBI treatment, a more effective intervention strategy.
- It does appear to protect against disseminated TB and severe forms of the disease that can occur after primary infection.
- It affords inconstant protection against pulmonary TB.
- It does not protect against TB reinfection or adult TB.
- Even if implemented under the best conditions, and assuming maximum efficacy, it has scarce impact on prevalence rates of disease and does not contribute to a reduction in the annual risk of infection. It does, however, have protective effects in children, and 95% of these cases are smear-negative with a minimal capacity to infect others.
- It has a potential risk of dissemination if the patient acquires HIV, although complications are rare.

**Contraindications to revaccination in schoolchildren**

At present, there is no scientific evidence to justify revaccination in schoolchildren or in children over the age of 5 years. Furthermore, if it is acknowledged that BCG vaccination only protects against severe TB in children, it must then be remembered that this protection will disappear if the child develops adult forms of TB. If it is still believed that the BCG vaccination has a protective effect in children above the age of 5 years, and for this reason it is decided to recommend revaccination in schoolchildren, it should also be accepted that it would also be necessary to provide further protection by revaccinating at a later age. Hence, following this erroneous premise, not only would revaccination have to be recommended in schoolchildren, but also every 5 to 10 years thereafter. If it is acknowledged that this would not be the case, then revaccination should not be administered to schoolchildren.

**Side effects of the BCG vaccine**

As described earlier, the BCG vaccine is prepared from live bacilli, which is why its use is associated with certain side effects. Although these side effects are generally rare, they vary greatly, from disseminated infection from BCG to death. Table 23 shows a classification of possible complications that may result from the vaccine. For this reason, if BCG vaccination is indicated as an intervention strategy by an NTP, the programme must consider the need to monitor the development of possible side effects. Evidently, the likelihood of side effects, in particular the more adverse effects, increases in immunodeficient children and those who suffer from severe malnutrition, which is a very common situation in poorer countries.

It is well known that intradermal BCG vaccination causes a primary reaction at the injection site. However, some individuals suffer an excessive
reaction, with ulceration, subcutaneous abscess, or suppurative adenitis. Despite the fact that BCG vaccination is practised widely and there is evidence of the poor evolution of vaccination lesions and generalised dissemination, it is not known what the risk of adverse effects is from the vaccination. This is mainly because local complications are not usually reported or diagnosed.

The IUATLD performed two studies to investigate the incidence of complications from BCG vaccination: a retrospective study (1975-1976) and a prospective study (1979-1981). Six European countries participated in the second study, which involved approximately 5.5 million vaccinated children, half of whom were over the age of 1 year when vaccinated. The observed risk of local complications and suppurated lymphadenitis was 387 cases per million in the younger age group, of which 93 per million registered positive histological or bacteriological results. In the older age group, the risk was 25 per million, and confirmation was attained in 18 cases per million. The risk of disseminated infection and hypersensitive reactions varied considerably amongst the countries. In the former German Democratic Republic, the risk ranged from 5.59 per million in children under the age of 1 year to 13.6 per million in children above this age. In Romania, the rates were 3.49 per million in those younger than 1 year and 0.99 per million in those above 1 year old. This major study suggested that both the number of notifications and risks calculated were underestimated, since there were cases of osteitis that were not recorded.

Table 23. Classification of possible complications caused by BCG vaccination

1. Abnormal primary reaction due to BCG vaccination:
   1.1. Ulcers, Koch’s phenomenon, abscess
   1.2. Regional purulent adenitis
2. Disseminated BCG infection; generalised or local lesions; non-fatal cases
   2.1. Osteitis
   2.2. Retropharyngeal abscesses
   2.3. Specific tuberculous-type cutaneous lesions: lupus, others
   2.4. Metastatic subcutaneous and intramuscular abscesses
   2.5. Bone and joint complications (including synovial lesions)
   2.6. Renal and urogenital complications
   2.7. Pulmonary and hilar complications
   2.8. Mesenteric adenitis
   2.9. Multiple adenitis and/or hepatosplenomegaly, or other locations
3. Disseminated BCG infection; generalised lesions; fatal cases
4. Post-vaccination syndromes or pathologies associated with BCG vaccination
   4.1. Chronic local cutaneous complications (keloids, histiocytomas)
   4.2. Acute cutaneous eruptions (erythema nodosum and other eruptions)
   4.3. Ocular complications
   4.4. Other syndromes; non-fatal cases
   4.5. Other syndromes; fatal cases
It has been observed that in certain BCG strains, the virulence and dose are more likely to cause bone and joint lesions. However, complications from regional ganglions are more related to the vaccine dose and the (younger) age of the child when vaccinated.

**BCG vaccination as an intervention strategy in the control of tuberculosis: indications according to the epidemiological situation**

Of the three possible community interventions for TB control—chemotherapy, chemoprophylaxis, and BCG vaccination—the strategy on which all efforts should focus is chemotherapy, followed by LTBI treatment in a distant second place, and, lastly, BCG vaccination. This order of priority is based on factors related to efficacy, action, speed of action, duration of effect, capacity to eliminate infection sources, and possible community benefit. These factors, applied to each of the three intervention strategies, are discussed in detail in the chapter on TB control.

Having discussed the reasons for placing BCG in third place as an intervention strategy, and having analysed its efficacy and many limitations, several questions remain: is BCG vaccination, which is so widely recommended, of any real use? How can its use be justified as one of the vaccinations recommended by the WHO in its expanded programme on immunisation? To answer these questions, it should be remembered that there are very different situations worldwide regarding TB prevalence and control. As in the case of treatment of LTBI, the indication for BCG vaccination differs greatly from one region to another, depending on TB endemic rates, achievements in disease control in recent decades, and available health resources.

*Indications in countries with high prevalence rates*

There is still a large part of the world population that lives in regions with high TB endemic rates, with a very high prevalence of disease and infection, and a probable annual rate of infection of over 1%. In these areas, the priorities are to reduce mortality from TB (2 million persons still die in the world from this curable disease) and to attain high cure and case detection rates, preferably for persons with positive smear microscopy. Here, there should be no doubt that there should be mass vaccination at birth for the entire population, not for the purpose of influencing the epidemiological impact of the disease, but rather to reduce the high infant mortality in these countries. In these areas, where 80% of worldwide TB cases live, BCG vaccination should become part of the intervention strategy, alongside chemotherapy (with
Directly observed treatment) and appropriate measures, to increase passive case detection.

**Indications in countries with moderate prevalence rates**

There is another significant segment of the world population that lives in zones of so-called moderate TB endemic rates, with an estimated annual rate of infection of 0.2% to 1%. Here, although it is likely that the problem of mortality has already been overcome, and the priorities should be on healing cases and increasing case detection, children are still at a high risk of TB infection, particularly those from the more socially and economically deprived sectors who have worse access to the health system. This is why in this group of countries, which consist of the great majority of middle-income countries, mass vaccination at birth should also be recommended, even though its impact on mortality will likely be lower and no epidemiological impact is to be expected.

**Indications in countries with low prevalence rates**

In the segment of the world’s population that lives in low TB endemic zones, with very low disease rates and prevalence of infection, the annual risk of infection is less than 0.1%. In these countries, which should already have attained success in the detection and healing of positive smear microscopy cases, much effort should focus on the early diagnosis of the disease, including negative smear microscopy cases; on achieving a 100% cure rate in TB patients; and on strategies to attack the TB endogenous reserve. Here, LTBI treatment should be implemented as an intervention strategy. As explained earlier, since BCG interferes with tuberculin test results and LTBI treatment management, mass vaccination at birth is not indicated. In these countries, which comprise most of the world’s industrialised countries, BCG vaccination should not be used to support the health system, which is indeed often the practice; rather, BCG vaccination should be an individual decision.

BCG vaccination could possibly be indicated in children with negative skin test results who have had close and prolonged contact with chronic TB patients, those who have not complied with treatment, and those with multi-drug-resistant (MDR)-TB and in whom no other prevention or control strategy can be implemented. It could also be indicated in members of risk groups with an annual rate of infection above 1% and in residents of countries where it is mandatory.
BCG vaccination in health care personnel

Some scientific societies also recommend BCG vaccination in health care personnel who are at high risk of MDR-TB transmission and in whom other control strategies cannot be implemented or have failed. Thus, the vaccination is currently recommended in health care personnel who are in contact with persons with MDR-TB, since the possible efficacy of LTBI treatment is unknown in this context. However, it should be noted that the possible efficacy of BCG vaccination in this group of professionals also has not been demonstrated and, in theory, is likely to be highly questionable.

Epidemiological criteria for suspending BCG vaccination

As discussed earlier, BCG vaccination has specific indications in certain epidemiological circumstances. When such conditions improve, the almost zero benefit of mass BCG vaccination does not justify the cost of this measure, the interference it causes with other intervention strategies (e.g., treatment of LTBI), or its side effects. Therefore, international organisations have reached the conclusion that mass BCG vaccination should be suspended in a country where any of the following epidemiological situations are found:
1. An average annual rate of cases of pulmonary TB with positive smear microscopy equal to or less than 5 cases per 100,000 inhabitants during the previous 5 years.
2. In children under the age of 5 years: an average annual rate of tuberculous meningitis of less than 1 case per 10 million inhabitants during the previous 5 years.
3. An average annual rate of infection of TB equal to or less than 0.1%.

Recommended reading


Chapter 14 - Childhood tuberculosis

Chapter summary
Childhood tuberculosis (TB), in comparison with adult TB, is clearly different in epidemiological development, clinical presentation, and diagnostic methods, particularly in children under the age of 5 years. The only similarity pertains to therapy, and even then only three drugs can be used in the first phase when treating children. For this reason, children should be managed at senior levels in National Tuberculosis Control Programmes and preferably be cared for in areas where a paediatrician is on hand.

Childhood TB almost always registers with smear-negative microscopy results, and it is therefore assumed that the condition is not infectious. Control of TB in this group of patients thus has little epidemiological impact in the community. However, childhood TB is always the result of recent transmission, and children represent a sentinel group for the consequences of poor TB control. Hence, epidemiological studies involving children are of utmost importance.

Childhood TB almost always proceeds from primary TB, meaning that in young children the disease frequently manifests with haematogenous and lymphatic dissemination. The low bacillary population often produces negative results in microbiological studies, which is why other indirect diagnostic methods are important. Diagnosis should be based on an overall evaluation of a series of epidemiological, clinical, radiographic, tuberculin, and microbiological criteria. Using these criteria, a scoring system can be drawn up for the purpose of diagnostic decision making and, frequently, for determining which therapeutic tests have to be used.

Perhaps the first key issue in this Chapter should be to define up to what age an individual can be considered a child, in order to distinguish the different forms of tuberculosis (TB). In the great majority of countries, paediatrics covers care up to the age of 14 years, which may be too high an age limit in the case of TB management. Children above the age of 5 to 7 years already reproduce adult forms of TB, with a higher occurrence of pulmonary involvement or cavitary TB, and the possibility of registering a smear-positive result. When differentiating between the management of childhood and adult TB, a marked difference is found in children under the age of 5 to 7 years, a difference that increases further with younger age. This chapter will therefore focus on the management of children under the age of 5 to 7 years.
The priority of all National Tuberculosis Control Programmes (NTPs) is the management of smear-positive cases, since they spread TB and perpetuate the epidemic. Because most cases of childhood TB are associated with smear-negative microscopy results, childhood TB is hardly ever a priority for control measures in an NTP and is thus often excluded from management in these programmes. However, although the level of infectiousness is not of epidemiological significance, childhood TB would probably reap the greatest benefit from appropriate individualised clinical management. Indeed, the children of today are the future of all countries.

The management of a child with TB differs in several major ways from that for adult TB. TB in children, in comparison with in adults, has a different clinical presentation, and the diagnostic methods also vary—this is especially so in children under the age of 5 years. The only similar characteristic is therapeutic management, except that fewer drugs should be used in the first phase, owing to a lower bacillary burden in children. For this reason, children should be managed at senior levels in NTPs, in contrast with the care provided to adults with smear-positive microscopy. Preferably, children should be cared for in areas where there is a paediatrician.

This chapter will discuss the conditions that characterise childhood TB, dividing these conditions into four major areas: epidemiological factors, clinical presentations, utility of diagnostic methods, and treatment.

**Epidemiology**

It is assumed that childhood TB, which almost always results in smear-negative microscopy, is not infectious, and if so, is much less infectious than adult TB. This low level of infectiousness means that childhood TB control is of little epidemiological relevance in the community and that its management is basically a result of clinical interest. However, childhood TB always reflects recent transmission, suggesting therefore that there is an infectious adult for every childhood case. This fact does acquire epidemiological importance and is significant for protecting public health. For this reason, TB in children is an indication of poor TB control in the community. In fact, children with TB represent a sentinel group for the advances of an NTP against the disease. Furthermore, epidemiological studies involving children are of tremendous importance with regards to the analysis of infection parameters, the disease, and mortality, as well as the observation of the presence of recent transmission. For example, if a drug resistance survey was performed in children under the age of 5 years who had TB (a difficult study
because of the low bacillary burden), not only would information on drug resistance be obtained, but also information on the number of resistant strains being transmitted in the community and the possible virulence of these strains. For this reason, this age group is ideal for performing tuberculin studies, which focus on assessing the prevalence of tuberculous infection in the community, and for estimating the extent to which TB is transmitted in the community.

The best example of children as the sentinel population for demonstrating the success or failure of anti-TB efforts can be found in global statistics for TB. Of the 8 million new TB cases that occur each year worldwide, 1,300,000 are children under the age of 15 years. Likewise, of the 2 to 3 million deaths due to TB each year, 450,000 are children in this age group. Furthermore, the severe impact of HIV in low- and middle-income countries affects children.

**Clinical presentations**

In the great majority of childhood TB cases, the disease proceeds from primary TB, which means that haematogenous and lymphatic dissemination is common. The marked tropism from lymphatic involvement in children under the age of 5 years is of particular importance, since this can lead to a severe form of adenopathy. Furthermore, in these cases, 65% to 75% of tuberculous adenopathies have an intrathoracic location, particularly with hilar and/or mediastinal adenopathy. The rest are extrathoracic. One particular manifestation is adenopathy affecting the cervical ganglionic chain, which is commonly referred to as scrofula. When scrofula affects children younger than 5 years of age, 75% to 80% of cases are caused by environmental mycobacteria and not *M. tuberculosis*. Studies reporting this finding, however, have all been conducted in developed countries; it is not known whether this is the case in countries with high TB incidence. The *M. avium* complex and *M. scrofulaceum* are the species that are most commonly involved in this clinical presentation, and they are known to be highly resistant to antituberculous drugs. Surgical removal is therefore indicated in these cases. For this reason, it is important to culture all biopsy samples from presentations that are compatible with scrofula, because if the culture confirms *M. tuberculosis*, medical treatment will suffice and it will not be necessary to resort to surgery.

Very young children, especially infants younger than 6 months, have an undeveloped cellular immune system and are therefore particularly sus-
ceptible to haematogenous dissemination and possible presentation of miliary TB. It is necessary to be on the alert for the possible development of meningeal TB, which is the most severe and fatal form that affects children.

Despite the above, the most common clinical presentation of TB in children is pulmonary TB, although, as mentioned, miliary and extrapulmonary TB is more common than in adults and therefore a keen diagnostic suspicion must always be maintained.

**Diagnostic difficulties**

While the diagnosis of adult TB is fundamentally based on microbiological studies, in childhood TB only a small percentage of these techniques are useful, which is why other indirect diagnostic methods are used more often in children. The lack of microbiological support makes the diagnosis of childhood TB far more difficult, and very often the diagnosis has to be based on other much less specific methods. This means that the diagnosis of TB can only be confirmed on very rare occasions, and it is therefore essential to possess an in-depth knowledge of what these indirect methods offer. Because a diagnosis cannot be confirmed, under- or over-diagnosis is a possibility, depending on the importance given to evaluation with alternative methods.

In short, the diagnosis of childhood TB should be based on an overall evaluation of a series of epidemiological, clinical, radiographic, tuberculin, and microbiological criteria. Using one of these criteria, a decision can be made to commence treatment and a therapeutic test may be performed to confirm cure.

**Epidemiological factors**

The frequency and importance of a focal point of transmission of the infection within the family to a child has been widely discussed in the literature. The World Health Organization considers contact studies to be one of the most practical methods of detection, especially in children. This means that when pulmonary TB is diagnosed in an adult, it is essential to examine all the children with whom the adult has had close contact. Likewise, whenever TB is diagnosed in a child, it is necessary to determine if there is an undiagnosed infected adult in the family. Finding the source of TB transmission becomes more important in countries with a low TB prevalence, since in these countries there are few infectious focal points in the community, and
a child with TB can readily lead to the suspected adult index case. In countries with a high TB incidence, where there are numerous infectious cases in the community, although there may not be a clear contact, it is also possible to determine who the contact source may be, with less room for error.

**Clinical criteria**

Clinical, physical, and analytical symptoms are unspecific and may provide very little aid in diagnosis. Furthermore, considering the significant degree of radiological involvement observed in many children with pulmonary TB, physical signs and symptoms are surprisingly rare. Clinical presentation depends on the location of the disease. The most common presentation in children is pulmonary TB, which initially manifests with dry cough, dyspnoea, sweating, and weight loss. Since clinical presentation is extremely unspecific in children, much more so than in adults, it is necessary to be on the alert for the possibility that a child may have TB when he or she shows signs and symptoms, such as cough, febricula, weight loss or absence of weight gain, irritability, or erythema nodosum. Miliary and extrapulmonary TB (i.e., in sites such as the lymph nodes, intestines, meninges, and bones) is more common in children and must also be considered. Findings on exploration are also very rare, except in newborns, who present with symptoms of chronic spastic bronchitis that do not respond to standard treatment. Manifestations of primary infection should be taken into account. Phlyctenular conjunctivitis and erythema nodosum may remain undiagnosed if they are not suspected. Blood tests provide very few findings. The erythrocyte sedimentation rate, which is highly variable at the onset of disease, may be useful in assessing disease evolution and treatment response in the initial months.

**Tuberculin testing**

As explained in Chapter 6, despite its limitations, the tuberculin test is actually one of the mainstays in TB diagnosis in children, and therefore any suspected cases should be confirmed by a positive tuberculin test. Owing to the importance of the tuberculin test in this population group, the test must be correctly administered and interpreted. Indeed, correct interpretation is essential, and the circumstances surrounding a child having to undergo the test should be carefully considered in order to detect a false-positive or false-negative result.
With regards to false-negative results, there are two very important conditions that must always be taken into account in children:

1. Recent infection. It takes 4 to 8 weeks for delayed hypersensitivity to be established after *M. tuberculosis* enters the host. During this period, the tuberculin test may yield negative results. This is the “window period”.

2. Severe forms of TB. It is common to find a negative result in miliary localisation and meningitis.

Other situations involving immune deficiency, whether congenital, acquired (HIV), or temporary, as in viral diseases; or use of corticoid or immunosuppressant treatment; may result in a negative tuberculin test. When a false-negative result is suspected, the tuberculin test must be repeated as many times as required; the test does not produce sensitivity.

False positives should be taken into account when assessing the tuberculin test, particularly with regard to reactivity to the tuberculin on the part of environmental mycobacteria and, above all, from BCG vaccination.

In children, the tuberculin test increases the positive predictive value considerably for the diagnosis of tuberculous disease. All positive tuberculin test results in children are the result of recent infection, and the greatest risk of suffering from the disease is found during the first weeks and months after the infection occurs. For this reason, the younger the child, the faster the infection is detected by tuberculin test, and there is therefore a higher probability that the disease is proceeding from a primary infection. A positive tuberculin test in a child is always an indication for intervention, either by administering treatment of latent tuberculous infection (LTBI) if active disease has been ruled out, or by administering treatment if the child is considered to have the disease. If there is any doubt as to whether the child has the infection or the disease, the best recommendation is treatment, particularly if there are compatible symptoms.

**Radiology**

In the diagnosis of adult TB, radiology should always be backed up with microbiology, owing to its lack of specificity. In children, radiology is of much greater significance and actually becomes an essential diagnostic tool. However, interpretation of radiographs is a highly complex matter.

In the pathogenic pattern, it has been seen that the infection commences by depositing bacilli in the alveoli. Lung parenchymal inflammation is not usually visible on the chest radiograph, but an unspecific localised infiltrate may be observed. All the lobar segments in the lungs are at the same risk
of being the initial focus of infection, and although there is usually just one focal point of infection, in 25% of cases there are multiple foci. In the initial phase, the infection disseminates to the regional lymph nodes. The characteristic lesion of initial tuberculous infection is a relatively large adenopathy, in relation to the relatively small size of the initial parenchymal focus. Because of lymph drainage, a focus in the left pulmonary parenchyma often causes bilateral hilar adenopathy, and a right-sided focus is accompanied by adenopathy on the same side.

Mild parenchymal opacities and adenitis often resolve spontaneously, occasionally with calcification, giving rise to the so-called bipolar complex if the calcification occurs in the inoculation chancre and to mediastinal adenopathy. In other instances, particularly in children younger than 3 years, because of the characteristics of the lymph system, the lesion progresses and causes much enlargement of the mediastinal adenopathy, which compresses the bronchi (extrinsic compression), in turn causing bronchial obstruction (Figure 16). When the adenopathy grows, it may infiltrate and break the bronchial wall, causing a granuloma in the bronchial lumen (intrinsic compression), which may also lead to obstructive problems. These granulomas may rupture in the bronchus, causing bronchogenic dissemination.

All these changes will have an effect on the chest radiograph, and may take on highly varied forms: atelectasis, hyperclarity, or mediastinal or parenchymatous limits. They may appear between chest radiographs, or change in the course of evolution. It is impossible to describe the appearance of a primary infection pattern since any abnormal image may have this aetiology. Correct interpretation by the physician is thus essential.

Sometimes there may be necrosis of pulmonary parenchyma, causing the formation of a thin-walled tuberculous cavity. Localised pleural effusion often accompanies the primary pulmonary focus, but significant pleural effusion is rare in children under the age of 2 years. Reactivated TB, as observed in adults, with typical thick-walled apical cavities, is very rare in children, although it can be found in teenagers.

It is advisable to take two radiographs: one anteroposterior and the other lateral on inspiration. Occasionally, it may be necessary to complement the study with computed tomography or magnetic resonance imaging. These techniques are contraindicated in the routine clinical management of these cases in low- and medium-income countries because of their high cost. Additionally, due to the high prevalence of TB in these countries, where an assumed diagnosis of active disease can be made with greater confidence, a therapeutic trial can be implemented without having to use further imaging.
techniques. However, in industrialised countries where similar symptoms may represent alternative diagnoses, computed tomography and magnetic resonance imaging may aid in the diagnosis. Indeed, computed tomography has frequently been shown to reveal mediastinal adenopathies in patients with suspected TB and a normal chest radiograph. It should be noted that many of these patients also have positive results by polymerase chain reaction (PCR) for *M. tuberculosis*.

**Microbiology**

The isolation of *M. tuberculosis* is that which confirms the diagnosis of pulmonary TB in the adult, but this measure frequently cannot be used in children because childhood TB is associated with a very low bacillary burden that does not yield a positive smear microscopy result. Still, microbiological studies should be performed in all cases of suspected disease.

The problems surrounding microbiological diagnosis of childhood TB are based on two major areas: the impossibility of obtaining appropriate study samples, and the low quantity of bacilli contained in such samples. Since children do not expectorate, especially young children, and they simply swallow secretions, gastric juice can be used instead, obtained through aspiration with a nasogastric tube. This procedure should be performed on a fasting child and on 3 consecutive days. The sample must be processed as soon as possible. Results of cultures obtained via this method vary greatly, from 14% to 41%. The disadvantage of the gastric lavage sample is that if the maximum yield is to be obtained, by collecting all secretions aspirated during the night, the procedure must be performed as soon as the child wakes up, because if there is a delay the secretions will be quickly absorbed in the stomach. For this reason, the child has to be admitted to hospital, which is a course that is rarely justified if the patient is not very ill, especially in low- and medium-income countries.

According to the most important studies, direct smear microscopy of the sputum or of gastric lavage is only positive in 5% to 10% of children with pulmonary TB, and the sensitivity decreases with the (younger) age of the patient. Sensitivity of the culture from sputum and gastric lavage does not exceed 50%, which is very low considering that it is necessary to wait several weeks to confirm the diagnosis. It may sometimes be necessary to return to sample taking by means of bronchoscopy, particularly if any obstructive process has to be ruled out. In this case, the bronchial exudate
and other suitable samples must be collected. The problem of diagnosis increases even more in extrapulmonary forms of TB, particularly meningeal TB.

**Therapeutic tests**

The decision to diagnose TB and recommend treatment is often based on indirect and relatively unspecific data. For this reason, a therapeutic trial is often initiated in a suspected case, i.e., by commencing an antituberculous treatment regimen and observing whether the child is cured. These therapeutic trials are more justified in low- and medium-income countries than in wealthier nations. In the latter, it is common to find an adult TB case in a contact study, since the epidemiological clues are of greater value (there are fewer infectious cases in the community) and there are more resources available to reach a diagnosis (e.g., computed tomography, PCR). Furthermore, because TB is less common in wealthier countries, it is necessary to resort to these diagnostic methods more frequently to rule out other possible conditions that may have similar signs and symptoms. In poorer countries with a high TB prevalence, it is more common not to find epidemiological clues. Further, there are fewer resources in these countries, and when the clinical presentation is suggestive of TB, it is indeed almost always the case because of the high prevalence of the disease in the community. This is why a therapeutic trial is much more justified and recommended in suspected childhood TB in low- and medium-income countries.

**Other diagnostic methods**

The possibility of employing other diagnostic methods has two purposes: to obtain better study samples and to increase the utility of microbiology. The possibility of resorting to gastric lavage or specimens obtained through bronchoscopy has already been commented on, in order to improve the quality of samples to be studied. Samples obtained via biopsy or aspiration in suspected extrapulmonary TB cases can also be considered.

PCR can be used directly on the clinical microbiological samples obtained in children. However, the sensitivity of a diagnostic PCR test ranges from 25% to 83%, but specificity is almost 100%. The reason is that a positive result with PCR in children cannot differentiate between recent infection and disease; this is one of the biggest disadvantages of this technique. Furthermore, a PCR test is very costly and complicated to perform and therefore cannot be indicated in low- and middle-income countries.
these countries, when confronted with a suspected case of TB, a therapeutic trial is recommended instead. A PCR test could be indicated in industrialised countries, mainly because these countries have more resources and because alternative diagnoses are more common.

The other method that was suggested earlier (in Chapter 8) as being able to contribute to the diagnosis of childhood TB is serology. Although it has very low sensitivity (less than 21% to 40%), the test yields few false positives in children. In addition, a positive serological test could provide strong support in diagnosing the disease. In any event, results obtained via this method must always be interpreted in conjunction with results of other tests.

The approach to tuberculosis diagnosis in children: scoring system

As explained earlier, both a thorough evaluation of all the diagnostic tools discussed and a management decision must be made. Because the decision must be individualised, the management of childhood TB should take place at a higher level than the management of adults with smear-positive results. To standardise the diagnosis of TB in children, which would facilitate management at the peripheral level in the health system, scoring systems have been devised to assess all the topics discussed in this chapter. These scoring systems aim to achieve a more or less close approach towards TB diagnosis in children. They are artificial diagnostic tools that may be both highly useful and, at the same time, the subject of debate. This is why when childhood TB is suspected, it is best to have the child evaluated by a paediatrician who can decide which approach to take.

Treatment and prevention

Treatment is the only similar characteristic between adults and children with TB, except that since children suffer from forms of TB with low bacillary populations, it is much more unlikely for them to have the bacillary load necessary for selecting naturally resistant mutants. This means that only three drugs—isoniazid, rifampicin, and pyrazinamide—can be administered in the initial phase in children and maintained in the continuation phase. The use of ethambutol is to be avoided, since its main side effect is altered visual acuity, which cannot be assessed in children. The other difference in the treatment of children is the need to adjust the dose according to weight. Doses for children are shown in Table 7. Fortunately, side effects are less
common in children than in adults, but if any occur they should be managed in the same way as for adults.

The best way of preventing childhood TB is through good control of adult TB. As explained, the level of infectiousness is very low in children and the epidemiological impact is therefore also very low. However, treatment compliance must be ensured until the patient is cured. The search for TB cases can be conducted at a passive level among children who present for consultation in the health system with signs and symptoms that are suggestive of TB. However, active searching for cases should also be conducted among contacts between the ages of 5 and 15 years who have positive smear microscopy (depending on the resources of, and level of TB control in, the country). Tuberculin screening or mass radiological studies in the healthy population are not justified, since they are very costly and inefficient.

In low- and medium-income countries, LTBI treatment should be administered in all children aged 5 to 15 years (see Chapter 13) who have been in close contact with patients with smear-positive pulmonary TB. In developed countries, before initiating LTBI treatment, the discriminatory element of the tuberculin test should be introduced, as recommended in Chapter 13. Finally, in all low- and medium-income countries, all infants should be vaccinated at birth in order to lower infant mortality due to severe forms of TB. This vaccination is not justified in countries with low endemic rates, as was explained in Chapter 13.

Recommended reading


Chapter 15 - Tuberculosis in the elderly patient

Chapter summary
Tuberculosis (TB) is much more frequent in the elderly than in any other age group. This is because the highest prevalence of *M. tuberculosis* infection is found in the elderly, such prevalence being cumulative in the course of a lifetime, and because a degree of natural immune deficiency develops with age, with a reduction in the number and function of the T-helper lymphocytes and an increase in the presence of T-suppressor cells, thereby augmenting the possibility of endogenous reactivation of TB disease.

There is controversy over whether elderly subjects present with different clinical and/or radiological manifestations, although the condition seems to be linked to the degree of possible immune deficiency. What is known, however, is that the utility of tuberculin testing decreases in this population group, while the performance of microbiological techniques is similar to that recorded in younger patients. It does seem to be accepted that the diagnostic delay is greater in elderly subjects—this phenomenon possibly conditioned by factors such as memory problems, mental confusion, isolation, and other concomitant diseases with similar symptoms—and there is an increased risk of contagion.

Treatment is the same and cure can be achieved in all cases, although in view of the additional problems typically found in elderly patients (other pathologies and treatments), close observation is required, with attention to possible side effects. Mortality due to TB is clearly greater in elderly patients and is also related to the possible immune deficiency, associated diseases, concomitant treatments, increased rates of treatment abandonment, and delays in establishing the diagnosis in the elderly.

In view of the above, an increased diagnostic suspicion of TB is warranted in persons over the age of 60 to 65 years.

Epidemiology

The age distribution of tuberculosis (TB) cases in a given community is an excellent epidemiological study parameter that reflects the effectiveness of the control measures implemented. It should be remembered that tuberculous disease is more common in population groups containing an increased number of individuals infected with *M. tuberculosis*. Thus, in countries that have effectively fought against TB in past decades, early diagnosis and the
healing of most TB cases has been achieved, thereby shortening the epidemiological chain of the disease by eliminating the infectious sources in the community. As a result, population cohorts born in the last four to five decades have had low community infection risks and very few infections have resulted. This is why in these countries (which include most industrialised nations), TB is essentially found in the older age groups, where there is a persistent presence of individuals with \textit{M. tuberculosis} infection—witnesses to the poor epidemiological and social conditions they had endured during their childhood when effective treatment measures were not yet available. In these elderly individuals, TB develops as a result of endogenous reactivation of the bacteria acquired in the past, which have remained in a latent or dormant state in the host for decades.

However, countries where no such effective TB control measures were employed in past decades continue to have numerous sources of contagion in the community, and the population cohorts born in these subsequent years represent high infection risks. As a result, infection and, consequently, disease have persisted. This is why in these countries, which include most low- and middle-income nations, TB is fundamentally found in younger individuals. In contrast to the situation found in more developed parts of the world, TB in poorer countries is more a consequence of progression of infection or of exogenous reinfection.

Nevertheless, the above considerations refer to absolute numbers of patients. All studies conducted in developing countries and that have reported a predominance of disease in young patients almost never express the figures in rates corrected per 100,000 inhabitants in each age group. This form of expression in absolute numbers is the most valid approach for comparison purposes. Not presenting data as corrected per 100,000 inhabitants can lead to the false belief that elderly individuals in poorer countries are relatively free of the disease. Normally, in countries with low- or middle- level incomes, there are clear discrepancies between the age distribution curve expressed in absolute numbers of cases (Figure 51) and the curve obtained when these values are corrected per 100,000 inhabitants in each age group (Figure 52). The example of the age distribution of new TB cases diagnosed in Honduras in 2000 (Figures 51 and 52) illustrates the differences between the two ways of presenting the data.

The elderly population is the sector of the community that suffers the most from TB, regardless of the development of the country or the efficacy of the antituberculous strategies employed in the past. However, life expectancy is lower in poorer countries (an average of 20 years less than in wealthier countries), as a result of which there are fewer elderly individuals. Still,
**Figure 51.** New cases of TB in Honduras in 2000. Distribution by age, in absolute numbers. The numbers next to the diamonds (♦) indicate the number of cases. Source: National Tuberculosis Control Programme of Honduras.

**Figure 52.** New cases of TB in Honduras in 2000. Distribution by age, in rates per 100,000 inhabitants in each age group. The numbers next to the diamonds (♦) indicate the rate per 100,000. Source: National Tuberculosis Control Programme of Honduras.
these elderly subjects have had to suffer even worse epidemiological and social conditions than their counterparts in the developed parts of the world, and, as a result, have a higher prevalence of *M. tuberculosis* infection and greater possibility of developing TB.

That the oldest segment of the population suffers tuberculous disease the most can be attributed to two reasons. First, the elderly have the highest prevalence of *M. tuberculosis* infection, since the prevalence is cumulative in the course of a lifetime. Thus, the older the individual, the greater the probability of infection. Second, immune defects in cellular immunity tend to be found with advancing age.

**Pathogenesis**

Estimations based on tuberculin anergy results from studies of elderly patients with TB infection or disease, and research involving animal models and healthy or TB-affected elderly individuals (in comparison with younger patients), have demonstrated the existence of the above-mentioned discrete immune deficiency in older individuals. This natural immune deficiency is most likely established after the age of 60 years, increasing in probability and in intensity with age. This defect may be related to a reduction in the number and function of T-helper lymphocytes, and to an increase in the presence of T-suppressor cells—together with a possible increase in humoral immunity.

The way in which the disease develops will depend on the epidemiological situation found in the different communities. Thus, in areas with high rates of TB disease and infection in young subjects, a high infection rate is to be assumed in the older age groups. Due to their immune deficiency, these older people are at a greater risk of developing the disease as a result of endogenous reactivation of the bacteria acquired in the past, and which have remained in a latent or dormant state in their bodies for decades. However, in some areas with lower rates of TB disease and infection in young subjects (e.g., industrialised nations), the prevalence of *M. tuberculosis* infection in individuals over the age of 60 years, while still comparatively higher, may not exceed 10% to 25% of the total. This percentage of infected individuals is at an increased risk of developing TB disease due to endogenous reactivation. Moreover, globally this age group shows increased sensitivity towards developing the disease through exogenous infection, as has been demonstrated in the nosocomial epidemics reported in developed parts of the world. Consequently, in these situations, if the elderly live in closed environments,
a case of TB (with its corresponding diagnostic delay) will cause many new infections by affecting a relatively immunodeficient segment of the population, and will considerably increase the risk of developing TB. In some homes for the elderly in developed nations, a TB disease rate of close to 7000/100,000 has been recorded, compared with the community rate of only 16/100,000.

Clinical manifestations and diagnosis

The immune deficiency characterising the elderly population might condition the growth and multiplication of *M. tuberculosis* and the different clinical and radiological presentations reported by some authors. Many studies have reported an increased frequency of disseminated forms of the disease (either demonstrated or suspected), with a clinical presentation in which syndromes of systemic involvement tend to predominate. However, this point remains open to controversy, as many authors have also reported no differences between young and older patients regarding the organs affected and the initial clinical syndrome involved.

Controversy likewise persists regarding the radiological presentation, with some studies reporting an increased frequency of lower lung lobe involvement and of non-typical or disseminated TB lesions. In contrast, other authors have reported no significant differences in comparison with TB found in younger subjects. This discrepancy in findings may have a pathogenic explanation based on the degree of immune deficiency found in the patients studied—a fact that has not been addressed in studies of clinico-radiological differences with respect to elderly TB patients. In this context, the greater the immune deficiency of the individuals, the greater the probability of disseminated presentations of the disease, systemic syndromes, and non-typical radiographic lesions. Furthermore, immune deficiency in the elderly is not only conditioned by old age but also by the frequent and numerous associated pathologies that are found in the elderly, and by the poorer living conditions and possible malnutrition in many instances.

Another characteristic of elderly TB patients is the increased diagnostic delay, which in turn implies an increased risk of contagion, particularly if the individual lives in closed institutions. Such delays in establishing a diagnosis can be attributable to a variety of reasons, such as memory problems, mental confusion, isolation due to partial loss of the senses (hearing, sight), and even the ability to communicate. However, the fact that elderly subjects
often suffer from other concomitant diseases with symptoms that are similar to those of TB still constitutes the main cause of diagnostic delay.

Some diagnostic techniques are less sensitive in the elderly. For example, tuberculin testing clearly loses its utility in both diagnosing disease cases and identifying infection—a deficit that is related to the onset of age-related immune defects. For this reason, in wealthier countries it is never sufficient to perform a single tuberculin test in the elderly (when studying infection or TB disease); in effect, a second or even a third skin test is needed (spaced 1 week apart) if previous results are negative. The aim here is to identify the possible booster effect that these tuberculin doses may exert upon immune memory loss—a procedure that has been shown to be effective in all studies involving elderly persons. This procedure is not indicated in countries with low- or middle-income levels, since in these regions the great majority of elderly persons are infected with M. tuberculosis and tuberculin testing is associated with many limitations (Chapter 6).

Regarding the performance of microbiological tests in the elderly, the results seem to be similar to those obtained in younger patients, provided the same types of lesions are involved. In studies showing an increased frequency of non-typical forms, with a greater presence of infiltrations versus cavitary lesions, the performance of smear microscopy and culture may decrease. Performance is thus related to the bacillary population of the lesions.

Lastly, some studies have described a different presentation of tuberculous granulomas in some forms of TB in the elderly, including the repercussions this may have for the histopathological study of biopsy specimens. Thus, a variant described in elderly patients is referred to as “areactive” TB, often with a miliary presentation. Here, the classic caseous granuloma is not surrounded by the usual abundant inflammatory cells, but instead by numerous bacilli. This form of presentation, attributed to an inadequate immune response, is most frequently seen with fever and weight loss, but without the typical pathological signs.

**Treatment and prognosis**

TB in the elderly is healed with the same treatment regimens indicated for younger patients, although some studies have described decreased efficacy of such treatments in the elderly. Other studies have described a longer time to negative culture conversion, again possibly due to the diminished immune support found in the elderly, although it is not known if a comparatively
lesser effect of treatment could also be involved. Elderly patients pose increased treatment adherence problems because of the possibility of memory lapses (difficulty remembering the prescribed dosage), mental confusion, a decreased ability to comprehend the scope of the disease and the precise drug doses required, and even eyesight problems that make it difficult to recognise which tablet to take. Some type of treatment supervision is thus required.

The most important consideration in the treatment of TB in the elderly is the increased toxicity of antituberculous medication in these patients, and the interactions of some of these drugs. The risk of liver toxicity, largely associated with isoniazid, is much greater in elderly patients (more than double the toxicity in younger individuals), as a result of which periodic liver function tests may be advisable. Similarly, nephrotoxicity is a consideration when streptomycin is used—a situation requiring monitoring of renal function and dose reduction. In addition, rifampicin has an enzyme inducer effect, and consequently the dosage of drugs commonly prescribed in the elderly (e.g., digoxin, antiepileptics, corticoids, tolbutamide) should be monitored closely.

Based on the above considerations, and despite the fact that healing can be achieved in all cases, TB mortality is clearly greater among elderly patients. In this population sector, mortality has increased in recent years, even in the developed parts of the world. This increased mortality is influenced by many factors, including some of those already mentioned above, such as immune defects, associated pathology, increased treatment abandonment, and delays in establishing a diagnosis.

**Control**

In view of the above considerations, an increased diagnostic suspicion of TB is indicated in people over the age of 60 to 65 years. This is the age group with the highest TB disease rates, in whom the clinico-radiological presentation, associated diseases, and different performances or yields of the diagnostic techniques imply an increased delay in diagnosis. This delay is not only of great importance in terms of public health (related to increased infectious periods), but also for the patient, which explains why TB is found with some frequency in necropsy-based studies. Such studies have reported a considerably greater frequency of TB among older population groups. On the other hand, the most important finding possibly is that almost half of these
TB cases identified at necropsy did not have the opportunity to receive treatment because the disease had not been diagnosed when the patient was alive.

**Recommended reading**

Chapter 16 - Tuberculosis and HIV

Chapter summary

The epidemiological impact of human immunodeficiency virus (HIV) infection on tuberculosis (TB) depends on four main factors: 1) the prevalence of HIV infection in the community; 2) the prevalence of TB infection, the risk of infection, and the infection trend among individuals between the ages of 15 and 49 years; 3) the transmission pattern of HIV infection; and 4) the risk of developing TB disease among HIV and M. tuberculosis co-infected individuals. Based on these variables, it can be seen why the impact of the acquired immunodeficiency syndrome (AIDS) on the problem of TB varies dramatically from the poorest nations (severe impact) to the richest parts of the world (little influence).

Immunosuppression induced by HIV can increase the incidence of TB via three mechanisms: 1) endogenous reactivation; 2) progression of recent infection; and 3) exogenous reinfection.

In turn, the diagnosis of these patients can be problematic, depending on the degree of immunosuppression at the time of diagnosis. In HIV-infected patients with reasonably good immune defences (CD4+ lymphocyte counts > 300 cells/mm³), diagnostic test performance will be similar to that in patients not infected with HIV. In contrast, in subjects with advanced immunosuppression, increased clinical and radiological diagnostic difficulties may be encountered, and both tuberculin test results and histopathological findings may be more complicated to interpret. Nevertheless, the microbiological tests afford similar performance, although maximum care is necessary to ensure that multiple, good samples are obtained.

Treatment is the same as with normal TB patients, although in view of the increased rate of complications and particularly of drug interactions in these patients, management by expert physicians is required. Special attention should be paid to the pharmacological interactions between antituberculous drugs (particularly rifampicin) and antiretroviral agents (especially protease inhibitors). Chemoprophylaxis is always indicated in such individuals and should preferably involve 9 months of isoniazid.

Throughout history, the human species has periodically been attacked by different microorganisms that have threatened its very existence. Some of these microorganisms, such as the agent causing tuberculosis (TB) or malaria, cause millions of deaths each year. Occasionally, the emergence or re-emergence of a microorganism can cause an unexpected and catastrophic pandemic of unpredictable consequences. During the twentieth century, two
such unexpected health care catastrophes occurred. The first was the influenza epidemic beginning in 1918 that caused approximately 25 million deaths throughout the world in the course of 3 years. The second is thought to have begun in the summer of 1981, when a man in the United States presented with an opportunistic infection due to a case of severe immunodeficiency that could not be explained at the time. It is astounding that the virus that subsequently became known as the human immunodeficiency virus (HIV) could spread so extensively in less than two decades, leading to so many infected and diseased persons and deaths. The speed at which HIV has spread is all the more surprising because the virus is not transmitted through the air or via the digestive tract, but through human interrelations, which in theory should have caused its spread to be slow in the community. At present, there is no place in the world where this pathogen is not found, and its future devastating effects are still difficult to estimate. These considerations suggest that the disease was probably already present for some time in the human species, perhaps in some poorer areas of the planet, such as sub-Saharan Africa.

It is difficult to imagine a microorganism better suited than HIV to function as an ally of *M. tuberculosis*. The virus selectively destroys or alters the function of precisely those immune cells that defend the host against Koch’s bacillus. Thus, the oldest of human infectious diseases, represented by TB, and the most recent pandemic to affect humans, represented by HIV, have combined their pathogenic effects to become the leading cause of death in large parts of the world. It is estimated that sizeable areas of the poorest countries will be literally deprived of their young populations in the coming decades as a result of the deadly association of these two pathogens.

The present chapter provides a detailed account of how these two epidemics are merging in the world, with a review of the pathogenesis, diagnosis, and treatment of TB associated with acquired immunodeficiency syndrome (AIDS). Some of these points have already been addressed in other chapters, as a result of which only the salient facts will be emphasised here.

**Confluence of two epidemics**

The AIDS epidemic is interfering with the natural balance that existed between *M. tuberculosis* and the host, which, even before the introduction of antituberculous treatment, favoured the human host. It is now evident that
resources for controlling TB are proving to be insufficient for averting a new epidemic of this disease on a global scale.

The epidemiological impact of HIV infection on TB depends on four main factors:
1. The prevalence of HIV infection and its trend in the community.
2. The prevalence of TB infection, the risk of infection, and its trend among individuals between the ages of 15 and 49 years.
3. The transmission pattern of HIV infection.
4. The risk of developing TB disease among HIV and M. tuberculosis co-infected individuals.

**Prevalence of HIV infection and its trend in the community**

Towards the end of 2002, the World Health Organization (WHO) estimated that over 42 million people worldwide were living with HIV infection/AIDS, and that this disease had already caused 26 million deaths. The number of AIDS cases continues to grow each year, although in 2002 there was an estimated 5.6 million new cases of HIV infection, a figure very similar to that recorded for 2000. The best indication of the devastating spread of this disease is possibly afforded by the fact that in both 2000 and 2002, 2.6 million people were estimated to have died of AIDS. Similar to TB, the global distribution of AIDS is very heterogeneous, with 95% of all cases being located in the poorest parts of the globe. Thus, both pathogens have gradually spread to the most vulnerable populations of the world. At the end of 2002, it was calculated that 70% of all cases of HIV infection/AIDS were confined to sub-Saharan Africa, 20% to Southeast Asia and the Western Pacific, and 5% to Latin America and the Caribbean. According to the predictions of the Population Division of the United Nations, between 2010 and 2015 the life expectancy of the populations in the nine African countries with the highest prevalence of HIV infection will be reduced by an average of 16 years. This adds another obstacle to the development of these countries, where poverty can be expected to increase owing to the weakening of the economically active stratum of the population.

The scenario is completely different in the industrialised world, where only 5% of all HIV infection/AIDS cases are found, together with 5% of the cases of dual HIV-TB infection (Figure 53). These countries possess the resources and infrastructure necessary to institute good National Tuberculosis Control Programmes. Owing to a unique set of circumstances, the association of these two pathogens in the developed world also does not have the
same effects as in poor countries, a topic that will be discussed later in this chapter. Moreover, since 1996, highly active antiretroviral therapy (HAART) has been available for the treatment of HIV infection. These drugs, however, are very expensive, and their use is largely confined to industrialised countries. HAART affords substantial and sustained increments in peripheral blood CD4+ lymphocyte counts, together with reduction of the plasma HIV viral load to undetectable levels.

Although it is well accepted that the HIV epidemic is completely out of control in the world, there is much that we still do not know, such as:
1. The number of HIV-infected individuals in the world, and the proportion that will develop AIDS.
2. The number of individuals with high-risk behaviours for HIV infection in the different countries.
3. The true efficacy of the preventive programmes designed to modify risk behaviours under different epidemiological conditions.

**Prevalence of tuberculous infection, infection risk, and its trends in subjects aged 15 to 49 years**

TB has been the principal plague of mankind since the first half of the twentieth century. As explained in Chapter 4, it is estimated that one third of the world population (close to 2 billion people) are infected with *M. tuberculosis*. In most developing countries, over half the adult population is infected, which represents an enormous reservoir from which new cases of TB disease may develop if these individuals suffer a deterioration in their immune defences.

The appearance of AIDS occurred during a bad epidemiological juncture in many countries, when there was still a high proportion of *M. tuberculosis*—infected individuals. Regrettably, in countries with a high prevalence, TB predominantly affects younger individuals between the ages of 15 and 49 years (Figure 51), which is also the age range at which persons are most vulnerable to HIV infection. Furthermore, the incidence of TB—the so-called annual rate of infection—is still extremely high and shows no signs of decreasing significantly in many poorer parts of the world. To illustrate these differences between the situation in the developed and developing world, take The Netherlands, for example, where the risk of TB infection decreased by 10% to 14% yearly in the last 40 years, as a result of which the infection prevalence is presently less than 0.5% in those aged 20 years and 15% in those aged 50 years. This suggests that it may become possible
Figure 53. World map showing the estimated distribution of TB cases infected with HIV. Data from WHO 1999.
to “eradicate” TB in a few more decades. In contrast, in some African countries, successive tuberculín surveys have shown the risk of TB infection to continue to be high (about 2-3%) in the last 10 years. Similar considerations apply to Asia, the largest reservoir of *M. tuberculosis*—infected individuals.

Thus, while TB remains completely out of control in most poor countries, in the developed world its prevalence has been declining for over two centuries, coinciding with improved socioeconomic conditions in the community. This drop has been particularly apparent in the past 40 years, with the possibility of curing all TB cases provided effective therapeutic strategies are implemented. However, while developed nations have instituted successful TB control programmes for the early detection and cure of patients during this time, developing countries have achieved little in the struggle against the disease—in fact, a large number of infective cases continue to appear that elude detection and healing. Consequently, the different population cohorts born in the past 40 years have been exposed to very different TB infection risks—a situation that in turn has contributed to the fact that while 80% of infected persons in the developed world are older than 50 years, in developing countries 75% of infected individuals are below 50 years of age. This difference in the distribution of infected subjects is influencing the added problem posed by HIV infection, since 90% of those infected with the virus are younger than 50 years.

In short, the gains associated with several decades of ensuring good TB control throughout the world have not been used advantageously. The mistakes of the past in relation to antituberculous measures are now exacting a high price in most countries, particularly with the appearance of the HIV epidemic.

**Dynamics of HIV transmission**

Three HIV transmission patterns have been described. Type I fundamentally affects homosexuals and intravenous drug users, and is mainly found in the United States and Europe. Type II involves heterosexual transmission. Type III is less well defined and corresponds to those parts of the world where the prevalence of AIDS is still low. All kinds of combinations of these patterns may be observed, and account for the important variations in HIV epidemiology seen in different parts of the world.

Type I transmission, particularly that affecting homosexuals with high-risk behaviours, is very unlikely to worsen the TB problem significantly, since it affects a population that often has a low and decreasing TB infection
prevalence. From the TB perspective, transmission among intravenous drug users is more dangerous, since this is an already weakened population with a higher prevalence of *M. tuberculosis* infection. However, in view of its limited magnitude, transmission among this group of individuals is likewise not believed to have a significant influence on the epidemiological trend of the disease in developing countries. Moreover, drug users can be regarded as a relatively self-limiting transmission group, since those who have been previously infected will ultimately die or control the disease with antiretroviral drugs. Still, it is difficult to predict an increase in the disease due to this group because new drug users tend to avoid the parenteral route out of fear of contracting AIDS. In turn, the campaigns developed for the prevention of AIDS among homosexuals with high-risk behaviour have been shown to be much more effective than similar campaigns targeted at heterosexuals.

In contrast, type II (heterosexual) transmission is having a considerable impact on the problem of TB, especially in countries whose young adult populations are already largely infected with *M. tuberculosis*. Type II transmission is presently the dominant pattern in Africa, Asia, the Caribbean, and some regions of Latin America, where 50% to 80% of prostitutes are already infected with the virus and where perinatal transmission is leading to an alarming increase in AIDS-related infant mortality. On the other hand, it is estimated that the time to double the number of AIDS cases is shorter in the case of type II transmission. However, the preventive measures (which are estimated to be able to reduce type I—mediated infection by 50%) would only afford a reduction of about 30% in the best of cases among those infected via type II transmission. This is in part due to the difficulty of identifying bisexual individuals, a situation that tends to be predominant in restricted societies, with a male-female infection ratio closer to 1—which also increases the risk of maternal-offspring transmission.

Unfortunately, heterosexual transmission is also becoming increasingly frequent in other countries with a high prevalence of TB infection among the sexually active adult population, to the point that the WHO indicates that heterosexual transmission of HIV is now the predominant form of transmission in the world. Theoretically, the greater the number of sexual relations with different persons, the greater the risk of HIV infection.

**Risk of developing tuberculosis among patients with HIV and *M. tuberculosis* co-infection**

By knowing the percentage of HIV-infected individuals and *M. tuberculosis*—infected subjects in the 15- to 49-year-old age group in a population, we
can estimate the proportion of individuals simultaneously infected with both microorganisms in the community.

HIV infection increases by 20- to 40-fold the possibility that an *M. tuberculosis*—infected individual will develop TB disease. It is estimated that 4% to 8% of co-infected individuals will develop TB disease yearly, as a result of which—depending on how long they live—it can be expected that about half of these subjects will fall ill with TB. The average increased survival of HIV-infected patients thus constitutes a new vital factor concerning the impact that the AIDS epidemic may have on the problem posed by TB.

In some countries, an increasing number of recently diagnosed *M. tuberculosis*—infected individuals are also infected with HIV, in proportions ranging from 30% to 60% in some parts of Africa, the United States, and Latin America. On the other hand, the proportion of AIDS patients presenting with some form of TB already exceeds 50% in some regions of Africa, reaching 20% in large cities in Latin America. Even in more developed countries, despite the very low tuberculous infection rates in the age groups believed to be free of risk, the number of HIV-infected individuals presenting with TB in groups such as intravenous drug users, immigrants, and ethnic minorities remains significant.

In this way, in some regions and particularly in certain groups of people, TB has become the main infection complicating AIDS. Not surprisingly, epidemiological studies are indicating an alarming increase in TB incidence in large parts of the world where the epidemic is far from under control. In some parts of Africa, for example, the incidence of TB has more than doubled recently.

Not surprisingly, the map illustrating the world distribution of cases of HIV and *M. tuberculosis* co-infection (Figure 53) indicates that 95% of dual-infected patients are from the poorest parts of the world.

**Impact of HIV on the prevalence of tuberculosis**

Based on these considerations, it can be seen that the impact of HIV on the problem of TB differs greatly throughout the world. In industrialised countries, which represent only 5% of the HIV problem and of the dual HIV-TB infection cases (Figure 53), HIV transmission is largely through homosexual relations and intravenous drug use. As previously mentioned, intravenous drug users constitute a relatively small closed group whose numbers tend to decrease. The measures designed for HIV control can be as effective among
homosexuals as in heterosexuals (the main transmission source in the developing world). Moreover, in developed countries, 80% of \( M. \text{tuberculosis} \)—infected individuals are over the age of 50 years, while 85% to 90% of HIV cases are under this age. Consequently, the two population groups with TB and HIV infection are unlikely to coincide, as a result of which the impact of HIV on TB has been (and can be expected to remain) limited in industrialised parts of the world. In contrast, developing countries are characterised by large numbers of individuals infected with both pathogens. Further, both \( M. \text{tuberculosis} \) and HIV are found to affect the same age groups, specifically the sectors of the population between the ages of 20 and 45 years. This and the unlimited pattern of (heterosexual) HIV transmission in these areas attest to the terrible impact that HIV has on the problem of TB. For example, in sub-Saharan Africa and some parts of the Caribbean where the prevalence of both diseases is the highest in the world, the recent substantial increase in TB cases has caused the already precarious health care services to fail, contributing to a severe lack of hospital beds, drugs, and personnel. There is no doubt that this situation will continue to worsen in the coming decades.

**Pathogenesis**

HIV is known to be a lymphotropic virus that infects and eventually destroys the CD4+ or helper T lymphocytes via the intervention of a glycoprotein in its envelope (GP 120) which is complementary to the CD4 receptor. The function of the infected lymphocyte is altered as a result, and the cell is no longer able to respond to soluble antigens or antigens bound to other cells, with a decrease in the release of interferon \( \gamma \), interleukin 2, and other macrophage-activating lymphokines. Moreover, the infected cells begin to express GP 120 on their surface, and bind via this viral component to other uninfected lymphocytes to form pathological syncytial cellular formations. HIV also infects macrophages and other phagocytic cells without destroying them, but instead compromising their functions; as a result, chemotaxis is reduced, along with the bactericidal potential against intracellular microorganisms.

These macrophages operate as true Trojan horses, transporting the virus to more inaccessible organs such as the central nervous system. It has been calculated that each HIV-infected individual who is not undergoing antiretroviral treatment reduces his or her CD4+ helper lymphocyte population by about 70 cells/mm\(^3\) each year—which in turn leads to a progressive decrease in cell-mediated immunity that facilitates the reactivation of intracellular
infections such as TB. This is how it has become established that HIV infection is presently the greatest risk factor for the progression of a patient with *M. tuberculosis* infection (recent or old) to actual TB disease.

Immune suppression caused by HIV can increase the incidence of TB via three mechanisms:

1. Endogenous reactivation from dormant foci derived from remote infections. This would be the most frequent mechanism that, in the absence of severe cellular immune defects, would lead to typical cavitary and bacillary TB presentations.
2. Progression of recent infection, with the development of more acute and atypical forms of TB, difficult diagnosis, and frequent haematogenous dissemination reminiscent of the more serious forms of primary TB in children.
3. Exogenous reinfections in subjects previously infected with *M. tuberculosis*, who, on losing much of their immune memory, would progress to manifest TB.

Molecular biological studies conducted in the last decade have pointed to the importance of infections, particularly of exogenous reinfections, in seriously immunocompromised AIDS patients with TB.

On the other hand, TB may exert a deleterious effect on the natural course of HIV infection. In effect, stimulation of CD4+ lymphocytes carrying dormant viruses may activate these viruses. In this sense, it has been seen that while TB responds equally well to chemotherapy in both HIV-infected and uninfected subjects, patients with AIDS who develop TB, with similar levels of immunodeficiency, have shorter survival.

### Diagnosis

The diagnosis of TB in patients infected with HIV may present certain difficulties, depending on the degree of immunosuppression at the time of diagnosis (see Chapter 7). In patients with reasonably good immune defences (CD4+ lymphocyte counts > 300 cells/mm³), diagnostic test performance will be similar to that in non—HIV-infected individuals. However, the situation becomes more complicated in those with advanced immune suppression.

Regarding the clinical manifestations (Chapter 7), if HIV-positive individuals have not yet developed significant immune deficiency, TB symptoms tend to be similar to those observed in the rest of cases. However, in the immunosuppressed AIDS patient, the initial manifestations tend to be non-specific, with a predominance of general symptoms (e.g., nocturnal
fever, asthenia, weight loss, peripheral adenopathies), a high likelihood of tuberculin test negativity, and significant involvement of extrapulmonary TB locations. All AIDS patients should therefore undergo thorough screening to identify TB disease or infection.

The utility of radiology in HIV-infected subjects again depends on the degree of immune suppression involved (Chapter 7). If immunosuppression is not severe and the patient was previously infected with the bacterium, endogenous reactivation of these bacilli is typically observed, with production of lesions typical of post-primary TB. If immune suppression is severe, any exposure to a source of contagion, and even endogenous reactivation, will encounter practically no opposition on the part of the host defences—resulting mainly in the production of lesions typically associated with primary TB, with frequent lymphatic involvement and haematogenous dissemination. In this latter group of patients, normal chest radiograph findings are common, and extrapulmonary involvement is frequent.

As with all cases of TB, the most important concern is to reach a firm diagnosis based on microbiological techniques. As a general rule, the performance of such methods will be similar to that performed in patients without HIV infection, although it is highly advised to obtain as many good-quality samples as possible. Thus, in AIDS patients, in whom disseminated TB is much more common, all possible samples should be considered for confirming the diagnosis, including specimens from sputum, urine, cerebrospinal fluid, and biopsies of different organs. In cases of severe immune deficiency and fever of unknown origin, three haemocultures for *M. tuberculosis* may be useful.

It should also be emphasised that in severely immunosuppressed AIDS patients, the information afforded by the histological study of biopsy specimens decreases, owing to the inability of these patients to generate granulomas in the face of *M. tuberculosis* aggression.

**Treatment and chemoprophylaxis**

HIV-infected patients should receive the same treatment regimen as uninfected patients. The only additional requirement is closer supervision, because of the increased risk of complications in the form of adverse reactions, intolerances, and drug interactions. Consequently, the management of such patients should be in the hands of physician specialists. Drug interactions between rifampicin and antiretrovirals, particularly protease inhibitors, should especially be noted. Presently, the use of protease inhibitors is not
practical in poorer countries owing to their high cost; however, prices are expected to fall in the near future, as a result of which their use will become more widespread. The possibility of such drug interactions must therefore be considered. The most important examples are presented in Table 24.

Another problem is the greater probability of relapses, which increase as the host defences weaken and are not able to prevent the multiplication of the latent bacteria that persist when TB is healed. In this setting, some have suggested that the best course of action would be to prolong treatment, or to maintain the patient on isoniazid for life. However, these measures are not justified. It would be reasonable to administer the same treatment as in immunocompetent individuals and to maintain close supervision and follow-up, as well as an increased suspicion for relapse. Some prefer to prolong the treatment to 9 months, particularly in patients who take longer to show culture negative conversion.

In turn, it has been demonstrated that intervention with chemoprophylaxis in subjects with dual HIV and TB infection is highly effective; as a result, there should be no doubts concerning the utility of such intervention in these subjects. In these cases, the efficacy of isoniazid treatment for 9 months has been confirmed. As was explained in Chapter 13, although evidence suggests that this group can also benefit from the regimen comprising 2 months of rifampicin and pyrazinamide, recent research has suggested that increased liver toxicity may be an adverse effect. For the time being, this regimen is not indicated. Some medical societies also recommend rifampicin for 4 months, although there is no firm scientific evidence to support this approach.

Table 24. Principal drug interactions between antituberculous medications and antiretroviral agents. Source: reference 16, Tusset, 2000

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Methadone</th>
<th>Rifampicin</th>
<th>Rifabutin</th>
<th>Clarithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT ddI</td>
<td>Can ↑Cp AZT</td>
<td>NDAR</td>
<td>NDAR</td>
<td>NDAR</td>
</tr>
<tr>
<td></td>
<td>↓57% AUC ddI</td>
<td>Space 2 h</td>
<td>NDAR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1-dose ddI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ddC</td>
<td>No data</td>
<td>NDAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d4T</td>
<td>↓23% AUC d4T</td>
<td>NDAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3TC</td>
<td>Unlikely interaction</td>
<td>NDAR</td>
<td>NDAR</td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>May require slight ↑MT</td>
<td>NDAR</td>
<td>NDAR</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>↓60% AUC MT Possible withdrawal syndrome.</td>
<td>Not recommended</td>
<td>NDAR</td>
<td>NDAR</td>
</tr>
<tr>
<td></td>
<td>↑MT dose of 8th-10th day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiretroviral</td>
<td>Methadone</td>
<td>Rifampicin</td>
<td>Rifabutin</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>------------</td>
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<td>---------------</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Could Tc MT</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Monitor CLM toxicity</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>≤60% AUC MT</td>
<td>Possible withdrawal syndrome.</td>
<td>Assess dose increase EFV 800 mg/day</td>
<td>Rb 450-600 mg/day or 2-3 times/wk</td>
</tr>
<tr>
<td></td>
<td>May require Idose MT of 8th-10th day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>In vitro: +30% AUC MT</td>
<td>Contraindicated</td>
<td>IDV 1000 mg/8 h and Rb 150 mg/24 h or 300 mg 2-3 times/wk</td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>In vitro: x2 AUC MT</td>
<td>Contraindicated</td>
<td>Rb 150 mg 2-3 times/wk</td>
<td>Adjust CLM dose if alt. renal function*</td>
</tr>
<tr>
<td></td>
<td>In vivo: ≤36% AUC MT</td>
<td></td>
<td>NDAR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idose MT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td>In vitro: NDAR</td>
<td>Contraindicated†</td>
<td>Contraindicated</td>
<td>NDAR</td>
</tr>
<tr>
<td>HGC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td>In vitro: NDAR</td>
<td>Contraindicated†</td>
<td>150 mg/day or 2-3 times/wk‡</td>
<td>NDAR</td>
</tr>
<tr>
<td>SGC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir +</td>
<td>≤40% AUC MT</td>
<td>RFP 600 mg/day or 2-3 times/wk</td>
<td>Rb 150 mg 2-3 times/wk</td>
<td>Probably NDAR</td>
</tr>
<tr>
<td>saquinavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>≤40% Cp MT</td>
<td>However, in most cases NDAR</td>
<td>NFV 1250 mg/12 h Rb 150 mg/24 h or 300 mg 2-3 times/wk‡</td>
<td>NDAR</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>≤Cp MT</td>
<td>Consider Idose MT</td>
<td>Rb 150 mg/24 h or 300 mg 2-3 times/wk‡</td>
<td>NDAR</td>
</tr>
</tbody>
</table>

* CiCr 30-60 ml/min: reduce 50%; < 30 ml/min: reduce 75% (max. 1 g/day).
† In 2 patients, the use of RTV/SQV 400/400 mg/12 h or 100/1000 mg/12 h allowed for therapeutic levels of SQV in association with rifampicin.
‡ In intermittent regimens, the use of rifampicin is preferred.

Lastly, in patients with severe immunosuppression as a result of AIDS, BCG vaccination is contraindicated, since the vaccine considerably increases the risk of complications, some of which are serious. However, after assessing the risks and benefits, mass vaccination of newborns is advised—without having to conduct the virus detection test—in countries where the prevalence of HIV infection is high.
As a final comment, it should be emphasised that TB is the most preventable and treatable of all the infections that complicate HIV, even though it is also the most contagious. On the other hand, since TB is one of the first infections to affect HIV patients, it can be regarded as a form of sentinel infection of HIV infection.

**Recommended reading**

15. Styblo K. Impacto de la infección VIH en la epidemiología mundial de la tuberculosis. 

16. Tuset M. Interacciones medicamentosas entre los antirretrovirales y los antituberculosos.  


18. World Health Organization/UNAIDS. *AIDS Epidemic Update.* Geneva, Switzerland:  
WHO/UNAIDS; December 1999.
Chapter 17 - Extrapulmonary tuberculosis

Chapter summary

From the initial phases of invasion of the human lung, *M. tuberculosis* can disseminate through the lymph vessels or bloodstream to any organ or tissue in the body. Extrapulmonary tuberculosis (TB) as a whole represents between 10% and 20% of all forms of TB in immunocompetent patients, although this rate is notably higher in those with some degree of immunodeficiency. The most common types of extrapulmonary TB, in order of frequency, are pleural, lymphatic, genitourinary, and joint; however, the disease does not spread from these sites.

In almost all cases, there is a primary pulmonary focus from which the disease may disseminate to adjacent sites, or via the lymph vessels or bloodstream to any part of the organism. Clinical symptoms will depend on the area affected by extrapulmonary TB. Symptoms are very non-specific and similar regardless of the location. This, along with the lower performance of diagnostic techniques when dealing with paucibacillary forms, means that greater importance is given to imaging techniques, even though there are no pathognomonic radiographic signs regardless of where the disease is located. Microbiological performance will depend on the quality of the samples taken; thus, if the diagnosis is uncertain, it will be necessary to perform a biopsy. Biopsy specimens must always be cultured in media for mycobacteria.

Treatment is the same as for pulmonary TB, although prolonged treatment in meningeal and joint TB, and in TB of the lymph nodes, is recommended by some. Under National Tuberculosis Control Programme conditions, the same initial treatment should be recommended for all patients.

From the initial phases of invasion of the human lung, *M. tuberculosis* can disseminate through the lymph vessels or bloodstream to any organ or tissue in the body. The epidemiology, frequency of presentation, pathogenesis, and performance of diagnostic methods in extrapulmonary tuberculosis (TB) differ from those of pulmonary TB. Only the treatment is the same, with the exception of a few specific details. The first part of this chapter will analyse the epidemiology, pathogenesis, diagnosis, and treatment of extrapulmonary TB, focusing on the aspects that differentiate this form of TB from pulmonary TB. The second part of the chapter will be a brief summary of the most common forms of presentation of extrapulmonary TB.
A global perspective of extrapulmonary tuberculosis

Epidemiology

Extrapulmonary TB as a whole represents between 10% and 20% of all forms of TB in immunocompetent patients, although this rate is notably higher in those with some degree of immunodeficiency. Indeed, 60% of severely immunosuppressed HIV-infected patients affected by TB may have extrapulmonary forms of the disease.

The most frequent location is the pleura, which, as will be explained later, is the site predominantly involved in young patients. This is followed by the lymph nodes, which also mostly affect those during the early stages of life. The next two most commonly affected sites are the urinary tract and joints. There are other much less common locations of extrapulmonary TB; these may affect any patient.

Almost all cases of extrapulmonary TB are associated with negative smear microscopy, and as such it is accepted that the ability to infect others is practically nil. For this reason, extrapulmonary TB is not considered an epidemiological priority for National Tuberculosis Control Programmes (NTPs). Only the individual stands to benefit, while the community receives very little (if any) advantage. Consequently, when a contact study is required in such cases, the sole objective is to discover the initial source that infected the patient with extrapulmonary TB. Nevertheless, all cases should be reported to the NTP.

Pathogenesis

In almost all cases of extrapulmonary TB, there is a primary focus in the lungs, which may or may not be visible on a chest radiograph. This primary pulmonary focus may disseminate via means of proximity (e.g., pleural TB), through the lymph vessels (e.g., lymphatic TB), or through the bloodstream (to any location). When the bacillus reaches these areas, there is a local immunizing action that, together with the metabolic conditions of the area (pH and oxygen tension), will determine whether or not the disease will develop.

With the exception of pleural and lymphatic TB, in the vast majority of cases of extrapulmonary TB disease, dissemination occurs via the bloodstream. This may occur at any moment the organism is under attack by \textit{M. tuberculosis}, even from the very first moments of primary infection. When TB is present in more than two locations, it is known as disseminated TB,
which is an extremely serious condition since it indicates that the host defences are unable to control the infection. The probability of developing disseminated TB increases in persons with a greater level of immunodeficiency.

**Clinical manifestations**

The clinical manifestations will depend on the area affected by the microorganism—the most common sites will be discussed below. All areas affected by the disease have a common denominator, i.e., the surprising nonspecificity of the symptoms produced. Thus, there is no pathognomic symptom or sign characteristic of TB in any location. In each of the organs or tissues affected, the clinical manifestations are generally insidious and similar to those caused by any other disease. For this reason, TB can frequently be included in the differential diagnosis of any clinical condition.

**Diagnosis**

The methods used to diagnose each of the possible forms of extrapulmonary TB are the same as those used in pulmonary TB, although it can be difficult to obtain valid samples in these patients. Furthermore, as these forms of the disease are paucibacillary, the performance of the different techniques is very low. These limitations, in addition to the fact that the clinical manifestations are generally very non-specific, means that imaging techniques take on greater importance and that it is often necessary to obtain biopsy samples for histological and microbiological study. All biopsy samples should be cultured in media for mycobacteria, and great care should be taken to ensure that the best possible samples are obtained.

It is necessary to culture biopsy samples since the mere discovery of caseating granulomas is insufficient to confirm a diagnosis of TB, although it can be accepted if the clinical manifestations and radiology are compatible. Other environmental mycobacteria may cause similar histological lesions. It should also be noted that granulomas might not be present in biopsy samples taken from patients with advanced HIV disease, since this typical lesion cannot be produced in patients with pronounced immunodeficiency.

If the sample is directly manipulated (e.g., involving abscess punctures, cerebrospinal fluid, biopsies), aseptic measures must be taken and the sample should be transported in a sterile container. The sample that is to be sent to the microbiological laboratory must not be fixed in place, but instead should
contain some drops of distilled water to prevent it from drying out. In the case of a patient with TB and HIV co-infection, it is important to send as many samples as possible (e.g., from sputum, urine, cerebrospinal fluid), as well as three haemocultures if the patient is severely immunosuppressed and has a fever of unknown origin.

Although radiology takes on greater importance in extrapulmonary TB, no location of TB presents a pathognomonic radiological sign of the disease, and as such the disease can never be diagnosed solely on the basis of a radiographic image.

**Treatment**

Although there are no in-depth studies describing the length of time needed to treat extrapulmonary forms of TB, there are also no microbiological bases contraindicating the use of the same treatment pattern that is recommended for pulmonary TB. The only difference is that the vast majority of extrapulmonary TB locations are associated with a reduced number of bacilli, meaning that it will be more difficult to select naturally resistant mutants. Consequently, some experts recommend prolonging treatment in patients with meningeal or joint TB, as well as in those with TB of the lymph nodes, while others have disputed this recommendation. For this reason, in an NTP setting the same initial treatment should be recommended for all patients.

**Pleural tuberculosis**

<table>
<thead>
<tr>
<th>Section summary</th>
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</thead>
<tbody>
<tr>
<td>The main way that <em>M. tuberculosis</em> reaches the pleural cavity is through the rupture of a subpleural caseous focus, in this case involving an immunological mechanism. The organism can also reach this area by dissemination through the bloodstream. The acute form is the clinical manifestation that is most often observed, and in the majority of cases this begins with non-productive cough, chest pain, and a high temperature. The chronic form is found predominantly in the elderly. A chest radiograph will generally show a small-to-moderate unilateral pleural effusion. One third of patients will also have radiographically visible parenchymatous disease. On the other hand, the tuberculin test is negative in one third of pleural TB cases, although the test will yield a positive result in a maximum of 8 weeks. A positive tuberculin test in a country where the disease is not endemic strongly points to a diagnosis of pleural TB, especially if the effusion involves a young person.</td>
</tr>
</tbody>
</table>
Tuberculous pleural fluid is serous and rarely haematic; it meets the criteria for exudate, has high protein levels, has glucose levels generally over 3.3 mmol/l (60 mg/dl), and the pH is always 7.3 or lower. The total number of leucocytes is generally less the 5000/l, with a predominance of lymphocytes, and the mesothelial cell count is reduced (< 1 per 100 leucocytes).

For a definite diagnosis, it is necessary to demonstrate the presence of \textit{M. tuberculosis} in sputum, gastric lavage, pleural fluid, or a pleural biopsy sample. The performance of microbiological studies involving pleural fluid and biopsy specimens is very low, which means that for the majority of patients it is necessary to carry out a pleural biopsy for both microbiological and anatomic-pathological study. The combination of microbiological and anatomic-pathological studies can lead to the diagnosis of pleural TB in 85% to 95% of cases.

Determination of adenosine deaminase (ADA) in pleural fluid and other ADA serosal fluids is important in the diagnosis of pleural TB. The test is highly sensitive and specific, and has a specificity and sensitivity of over 95% in countries where the disease is highly endemic, with a certain number of false positives detected in metapneumonic effusions, empyemata, rheumatoid arthritis, lupus erythematosus, and lymphomata.

Treatment is the same as that used for pulmonary TB. However, it is worth noting that two thirds of pleural TB cases will spontaneously evolve towards a cure, although these patients will have a higher probability of developing another form of TB in the years to come. Neither steroids nor repeated thoracocentesis have any effect on the development of possible complications.

A pleural condition caused by TB is relatively common. Its presentation is linked to the endemic rate in the area; as such, it is fairly common in poor countries but extremely rare in industrialised nations. As there are differences between this form of TB and pulmonary TB, it is necessary to define its pathogenesis, clinical manifestations, diagnosis, and treatment.

Pathogenesis

The principal way that \textit{M. tuberculosis} reaches the pleural cavity is through a rupture of the subpleural caseous focus, in this case involving an immunological mechanism. It seems likely that with the arrival of the bacillus with its antigen protein components, a delayed hypersensitive reaction occurs, stimulating the T lymphocytes. The T lymphocytes, which can be found in the pleural fluid, release specific lymphokines, which may alter the permeability of the pleural vascularisation and induce the formation of granulomas.

The pleura can also be affected by other mechanisms, above all if the disease is disseminated through the bloodstream. It is also possible for the
primary focus to be reactivated; this is particularly common in older, immunocompromised patients. In children and young adults, pleural involvement is more likely to be the first manifestation of TB, occurring in the months after the primary infection.

Pleural TB is more common among young people, although up to 40% of some series are found in people over the age of 40 years.

**Diagnosis**

**Clinical manifestations**

The acute form is the most common clinical presentation, and in the majority of cases early symptoms include a non-productive cough, chest pain, and a high temperature. The chronic form is found predominantly in the elderly, in whom it is more common to find systemic symptoms such as asthenia, anorexia, and weight loss, accompanied by a slight fever, cough, and chest pain.

**Radiology**

A small-to-moderate unilateral pleural effusion is generally seen on chest radiograph (Figure 20). One third of patients will also have radiographically visible parenchymatous disease, which will be located in the same hemithorax as the effusion in the majority of patients. The amount of fluid is rarely significant, although in some series up to 4% of the massive effusions are caused by TB.

The other imaging techniques are of very little use when diagnosing pleural TB. Occasionally, computed tomography may reveal whether atelectasis or parenchymatous disease exists in the case of massive effusions.

**Tuberculin skin test**

The tuberculin test is negative in one third of patients with pleural TB, although the test will usually yield positive results if repeated within a period of no more than 8 weeks. One explanation for this phenomenon is that there are circulating monocytes during the acute phase of the disease, and these monocytes are known to be suppressors as they interfere with the sensitivisation of the T lymphocytes in the peripheral blood and skin but not in the pleural fluid. Other authors believe that this tuberculin anergy is a result of the sequestration of specifically reactive lymphocytes in the tuberculous tissues.
A positive tuberculin test in a country with low endemic rates strongly suggests a diagnosis of pleural TB, especially if the effusion affects young people.

**Biochemical study of pleural fluid**

Tuberculous pleural fluid has serofibrinous characteristics. It can sometimes be serosanguinolent (10%), but rarely haematic. It meets the criteria for exudate, with a high total protein concentration (a level > 50 g/L [5 g/dl] is indicative of disease) and glucose levels generally over 3.3 mmol/l (60 mg/dl), although this figure may be lower in approximately 20% of cases. Low glucose concentrations are frequently associated with concomitant empyema, a delayed diagnosis, or advanced disease with pleural fibrosis. It is not unusual for glucose concentrations to be lower than 1.1 mmol/l (20 mg/dl). The pH, which is generally 7.3 or lower (similar to the neoplastic effusions), is very variable and is of little help in diagnosis. It generally ranges from 7.00 and 7.29. However, a pH of more than 7.40 is not compatible with this aetiology.

**Pleural fluid cellularity**

The total number of leucocytes is generally less than 5000/l. When a differential recount is carried out, more than 50% of the total leucocytes correspond to mature lymphocytes, although a percentage of more than 80% is highly suggestive of TB. Polymorphonuclear cells may predominate during the first phase of infection, in response to the entry of bacilli in the pleural cavity, but these cells will be rapidly replaced by mononuclear cells. A diagnosis of TB is certain when it is observed in a short period of time that the polymorphonuclear cells are substituted by mononuclear cells in the cellularity of the pleural fluid. Eosinophils are rare, with numbers generally lower than 10%.

The number of mesothelial cells is reduced in a pleural TB effusion. Generally, there is less than one of these cells for every 100 leucocytes, while with other pleural aetiologies this number is generally more than 5 for every 100 leucocytes. This absence of mesothelial cells has been attributed to the fibrinogenous layer covering the pleural surface, which prevents the cells from shedding.

**Microbiology**

To diagnose pleural TB with certainty, it is necessary to demonstrate the presence of *M. tuberculosis* in the sputum, gastric lavage, pleural fluid, or
pleural biopsy specimen. The smears and the sputum and gastric lavage cultures may help confirm the diagnosis, although these rarely yield positive results unless there are parenchymatous lesions that can be seen on a radiograph.

The performance of microbiological studies on pleural fluid increases with the amount of fluid studied, and it is generally accepted that ideally 1 litre should be processed. A direct smear microscopy of this sample will be positive in less than 10% of patients, and the culture, depending on the series, will show evidence of the growth of *M. tuberculosis* in 11% to 70% of these cases. The low sensitivity of the smear and the excessive delay associated with culture means that it is necessary to carry out a blind pleural biopsy for many patients, a simple technique that is associated with low morbidity when using needles that are currently available. This procedure is especially necessary if it is not possible to determine the presence of adenosine deaminase (ADA) in the fluid. In addition, since paucibacillary forms of TB are involved, genetic amplification techniques (e.g., polymerase chain reaction [PCR]) may be very useful in the diagnosis (see Chapter 8).

Direct microscopy of the pleural biopsy specimen shows acid-alcohol—resistant bacilli in 14% to 34% of cases; in comparison, the culture is positive in 44% to 80%. Performance improves with a second and third biopsy, with regards to both the microbiological and anatomic-pathological study.

**Histopathology**

A diagnosis of pleural TB can also be accepted if granulomas are discovered in the pleural biopsy sample. These may appear in 50% to 87% of patients who have undergone a blind pleural biopsy. Nonetheless, pleural granulomatosis is not exclusive to TB, as other diseases such as sarcoidosis, rheumatoid arthritis, fungal infections, other mycobacteriosis, and even infections caused by *Francisella tularensis* may sometimes be the cause.

Fifteen percent of patients with pulmonary parenchymatous disease caused by *M. intracellulare* may present with pleural effusion, an occurrence that also applies to 3% of the mycobacteriosis caused by *M. kansasii*, and to 5% of the other diseases caused by other mycobacteria. These pleural afflictions may be confused with TB because pleural granulomatous inflammation is also observed, and because these mycobacteria are also shown as acid-alcohol—resistant bacilli on direct smears. Only cultures of this material can yield a definite diagnosis, although it is important to note that these mycobacteria do not lead to pleural involvement without also causing a pul-
monary parenchymatous disease, and as such can also be diagnosed by pro-
cessing the samples from the respiratory system.

Despite the above, more than 95% to 98% of cases in which granulo-
mas are observed in the anatomic-pathological study of the pleural biopsy
specimen involve TB, and this percentage is even higher if the granulomas
have caseating necrosis.

By combining the microbiological studies of the fluid, pleural biopsy,
and anatomic-pathological study of the biopsy specimen, a diagnosis of pleu-
ral TB can be established in 85% to 95% of cases. In the remaining 5% to
15%, this diagnosis can often be assumed. Nevertheless, if these data do not
suggest TB, or if there is any doubt about the diagnosis, a videothoracoscopy
and biopsy of the suspicious areas will be indicated. If these samples are
negative in the histological and microbiological studies, a diagnosis of pleu-
ral TB can be ruled out.

Adenosine deaminase and other determinants in pleural tuberculosis

Over the last two decades, a series of diagnostic tests involving pleural fluid
has been developed. The determination of ADA in pleural fluid and other
serosal fluids (see Chapter 8) has been shown to be particularly useful. This
enzyme, which intervenes in the catabolism of purines and whose main
physiological activity takes place in lymph tissue, has high levels of sensitiv-
ity and specificity (over 95% in countries where the disease is highly
endemic), with a certain number of false positives detected in metapneu-
monic effusions, empyemata, rheumatoid arthritis, erythematous lupus, and
lymphomata. Concentrations of ADA in the pleural fluid of over 43 to 45
U/l are associated with a sensitivity of 100% and a specificity of 95%.

The use of ADA has been sufficiently validated in several studies and
can now be accepted as a routine technique in the diagnostic algorithm for
pleural TB. It is important to bear in mind that the sensitivity of microbiologi-
cal techniques in TB of serosal fluids is very low; therefore, when faced
with a suggestive clinical manifestation and radiograph and a positive ADA
test, a diagnosis of TB can be accepted. This is especially true in regions
where it is not possible to perform a pleural biopsy. Measurement of ADA
is not difficult to perform nor is it very expensive, so having reference
centres in some low- and middle-income countries (depending on the pop-
ulation) that can perform determinations of this enzyme should be consid-
ered. ADA measurement is not indicated in poorer countries where there are
limited resources and high TB endemic rates. In such countries, when there
are clinical and radiological manifestations suggestive of TB, empirical treatment should instead be started.

Another test that has proved to be useful in the study of pleural TB is the determination of lysosome (muramidase) in the fluid and, above all, the coefficient of this with the level of lysosome in serum. Thus, a coefficient of more than 1.2 has excellent sensitivity (100%) and specificity (95%), with some false positives caused by empyemata and rheumatoid arthritis. Nevertheless, more studies are needed to validate this technique before it can be recommended as a routine procedure.

As the proportion and absolute number of T lymphocytes in tuberculous pleural fluid increase with respect to those found in the blood, the number of lymphokines produced also increases. One of these lymphokines, interferon \( \gamma \), has also been shown to be a useful parameter in the diagnosis of pleural TB.

Lastly, there has been evidence that some tumour markers, such as immunosuppressive acidic protein and \( \alpha_1 \)-acid glycoprotein, have considerably higher levels in tuberculous pleural fluid in comparison with neoplastic pleurisies. The determination of any of these parameters is not indicated in low- and middle-income countries.

**Diagnosis of complications**

Occasionally, infection of the pleural space by *M. tuberculosis* may lead to empyema. This may at times appear to be a complication of the parenchymatous disease, especially in the case of cavitary forms located in the upper lobes. This empyema is often associated with a bronchopleural fistula, as it is unusual for the empyema to drain, thus forming a fistula of the thoracic wall (*empyema necessitatis*). It is more common to find other infecting bacteria besides *M. tuberculosis*, in particular all gram-negative bacilli and *Staphylococcus aureus*, growing in the cultures of the pleural fluid.

A diagnosis of bronchopleural fistula is suggested by the development of water-air levels in the pleural cavity which can be seen on the chest radiograph. Injecting methylene blue or radioopaque material into the cavity and recovering it in the expectoration can confirm this.

**Approach to the diagnosis of pleural tuberculosis**

When the microbiological and anatomic-pathological studies of the pleural fluid and biopsy are negative, empirical treatment can begin in certain
patients while awaiting the cultures, even if these also prove negative. Thus, in patients under the age of 40 years who have a positive tuberculin test and whose pleural fluid corresponds to an exudate with a predominance of lymphocytic cells, antituberculous therapy may well be indicated. This indication is even more justified in low- and middle-income countries, or if the presence of ADA has been determined. On the other hand, if TB is suspected in an effusion that appears in a patient older than 40 years with risk factors for bronchogenic carcinoma and in whom studies of pleural fluid and blind pleural biopsy are negative, a pleuroscopy before starting empirical treatment is indicated.

**Treatment**

Two thirds of pleural TB cases will spontaneously evolve towards a cure. Nevertheless, in the case of these patients who are cured without receiving treatment, there is a high probability that pulmonary parenchymatous disease will appear during the following 6 to 12 months. Likewise, it has been found that 50% to 70% of patients who do not adhere to their treatment correctly will develop pulmonary TB or TB in another location in less than 5 years.

The treatment used for pleural TB is no different than that for TB of other locations, with the exception that, since it is a form of TB that has very few bacilli, it is difficult to select resistant mutants. This is why it may be advisable to omit a fourth drug during the first phase. Under NTP conditions, the same treatment as that for pulmonary TB should be recommended so as to facilitate the indications and follow-up. In addition, as has been explained earlier, the patient may also have a pulmonary parenchymatous condition, although this may not be visible.

Once treatment has begun, fever will generally disappear within the first 2 weeks, although this may not occur until 6 to 8 weeks later. The effusion may take up to 3 or 4 months to clear up; however, in the majority of cases it will do so in less than 6 weeks. In any event, this does not mean that the treatment should be changed in any way.

Some controversy surrounds the possible beneficial effect of corticosteroids in the treatment of pleural TB. It seems that corticosteroids merely cause symptoms to improve earlier and resolve the effusion more quickly, but they do not reduce the possibility of long-term sequelae. These agents have been described to decrease pleural thickening in the first 2 to 6 months of the disease. Therefore, corticosteroids are only indicated in the short-term if the symptoms are intense or the patient is gravely ill. They should never
be administered in the long-term to reduce the sequelae of the disease. Still, it is important to remember that these sequelae are uncommon and negligible if correct treatment is initiated.

Therapeutic thoracocentesis or repeat aspiration of fluid offers no advantages regarding the decrease or resolution of the disease, nor does either technique have any impact on the sequelae on pulmonary functions. Nevertheless, in the case of massive effusions, thoracocentesis may be considered. As with other infectious pleurisies, it is necessary to wait a minimum of 6 months before evaluating the sequelae and their possible surgical treatment.

In the case of a bronchopleural fistula and/or empyema, apart from antituberculous chemotherapy, it is necessary to insert a chest drainage tube. In patients in whom pharmacological therapeutics have made the sputum cultures negative, decortication is required if the fistula remains. In such cases, intervention can be extremely serious and the operation is associated with high mortality. Pulmonary expansion will not be possible in certain patients due to the severity of the parenchymatous affection; thus, it is frequently necessary to perform a thoracoplasty to fill the pleural space.

A patient suffering from pleural TB does not need to be isolated from others. Isolation is only necessary in the case of parenchymatous disease with a positive result to direct smear microscopy of the sputum. Even in this event, the patient may remain at home unless the severity of the process indicates otherwise.

**Lymph node tuberculosis**

**Section summary**

Lymphatic TB can be divided into two main groups: the first affects the peripheral lymph nodes (scrofula), and the second affects the internal adenopathies. TB of the peripheral lymph nodes affects the adenopathies in the head and neck principally, although it can affect any other area. The most important differential diagnosis should consider lymphadenitis caused by other mycobacteria. In children, *M. tuberculosis* is isolated in only 10% to 20% of peripheral lymphadenitis cases, increasing to 90% in adults. This entails different therapeutic routes and underlines the importance of culturing the biopsy samples or aspirates obtained from these locations. TB of the internal lymph nodes is generally a complication of primary TB. When it affects the mediastinum, the most common location, large adenopathic masses may be formed, which may compress and even perforate the tracheobronchial tree.
The treatment of lymphatic TB is the same as that for pulmonary TB, although some experts advocate prolonging the treatment for up to 9 to 12 months. One problem is that the size of the adenopathies decreases very slowly (over weeks or months), and in 5% to 10% of cases they are still the same size after the treatment has ended. This, however, does not mean that the treatment was unsuccessful. Surgery may be indicated in cases of lymph node TB caused by other mycobacteria, and when the mediastinum has been affected and is extremely compressive.

Owing to the high frequency with which *M. tuberculosis* disseminates through the lymph vessels, lymphatic TB is one of the most common forms of extrapulmonary TB presentation. Lymphatic TB can be divided into two main groups: the first affects the peripheral lymph nodes (scrofula), and the second affects mainly the internal adenopathies.

TB of the peripheral lymph nodes mainly affects the adenopathies in the head and neck, although it can affect any other area. The most important differential diagnosis must consider lymphadenitis caused by environmental mycobacteria. *M. avium* complex is isolated in 70% to 80% of cases of lymphadenitis. In Australia and the United States, the second most common cause is *M. scrofulaceum*, while in Northern Europe it is *M. malmoense*. In children, *M. tuberculosis* is isolated in only 10% to 20% of cases of peripheral lymphadenitis caused by mycobacteria, with *M. avium* and *M. scrofulaceum* isolated in the remaining instances. When an environmental mycobacterium is isolated, it can be argued that the form of entry and dissemination was not via the respiratory system, but via foci in the mouth, with the mycobacteria disseminating to the regional lymph nodes from there. *M. tuberculosis* is isolated in 90% of adults with this clinical manifestation. Awareness of the epidemiological differences between adults and children is of great importance since the vast majority of environmental mycobacteria that cause lymphadenitis in children are very resistant to antituberculous drugs. Furthermore, because this is a localised disease, surgical excision is indicated. However, in both adults and children in whom *M. tuberculosis* is isolated, this surgery is contraindicated and medical treatment is preferred. This evidence underlines the importance of culturing the samples obtained from a biopsy or by aspiration using a thin needle (the only way to obtain a definite diagnosis), rather than just sending these specimens to the laboratory for anatomic-pathological analysis.

For quite some time TB has been known to affect the lymph nodes. It was during the 1950s that involvement of the mediastinal lymph nodes in TB and its complications was first described, and that the earliest studies regarding the indication of surgery when the disease presented in this form
were published. Involvement of the lymph nodes is usually a complication of primary TB. Perhaps for this reason and because there would seem to be greater lymph involvement in younger TB patients, this condition has been traditionally described in children (Figure 16). At present, with the HIV epidemic, it is also quite common to find adults affected by this syndrome and with a pronounced cellular immunological deficit (Figure 31). Lymph node TB involving other sites such as the abdomen has been described in these patients. Large adenopathic masses may be produced in the mediastinum, which can compress and sometimes perforate the tracheobronchial tree. This process was considered relatively common in the past, especially before the advent of chemotherapy, with compressive symptoms reported in 67.8% of patients studied and bronchial perforations in 27.8%. Currently, with the availability of bactericidal treatments, this form of TB presentation and its complications is considered to be rare. Nonetheless, not everyone is in agreement with this belief, and certain series have been reported quite frequently. In these cases, early diagnosis is important, since aggressive treatment approaches will often be necessary to avoid complications.

Involvement of the abdominal lymph nodes by TB is common, and adenopathies can normally be found in various sites. These vary in size and the pathology can be studied with computed tomography, which will provide information regarding the size, location, and density of the adenopathies. Computed tomography will frequently be the method chosen in the case of HIV-infected patients as it provides information on all the regions affected. In patients with intestinal symptoms, it can help to discriminate among alimentary, mesenteric, and extraintestinal involvement. Findings are non-specific and a biopsy should be carried out, which can be complemented with use of imaging (an ultrasound scan or tomography). The adenopathies may obstruct the alimentary canal, urinary tract, or biliary tract (when their location is periportal or peripancreatic).

Biopsy samples must be obtained from the affected areas and then sent to the microbiological laboratory where a smear microscopy and culture can be carried out, as well as to the anatomic-pathological laboratory. Study of aspirate obtained using a thin needle to puncture the peripheral areas, or using a bronchoscope to obtain samples from the mediastinal lymph nodes, has also been shown to be useful.

Lymphatic TB should be treated in the same way as pulmonary TB, although some experts recommend prolonging treatment for up to 9 to 12 months, while others are in favour of maintaining treatment for the same length of time. One problem is that it is difficult for antibiotics to reach the lymphatic area, and the size of the adenopathy is largely due to a local immunological reaction. Consequently, adenopathies decrease in size extremely.
slowly (over weeks or months), and in 5% to 10% of cases they are still the same size after the treatment has finished, although this does not mean that treatment was not successful. At the end, 5% to 10% will be considered cured, and the residual adenopathies will remain. Even after appropriate treatment, these residual adenopathies may increase in size, leading to apparent reactivations. If the adenopathies fistulate during treatment that is adequate and correctly followed, this does not indicate that treatment is not working.

Surgery is not only indicated in cases of lymph node TB caused by environmental mycobacteria, but also in mediastinal involvement that is compressive as a result of these adenopathies, as well as in cases where the lymph node mass finally perforates the tracheobronchial tree. The predominantly endobronchial lesions may be tributaries of the endoscopic treatment (granuloma resection). From a technical point of view, the most important surgical manoeuvres are the opening and curetting of the adenopathies. Attempts to dissect or extirpate are not justified when there are no important inflammatory adherences, as this may cause serious vascular accidents. Likewise, pulmonary resections are not indicated unless there is irreversible parenchymatous damage. In any event, surgical treatment of mediastinal lymph node TB must always be evaluated when complications exist, as this will solve the serious compression of the tracheobronchial tree. In these cases, surgery may prevent residual endobronchial lesions, which invariably lead to secondary evolutive complications. The morbidity and mortality associated with this type of surgery is almost nil.

**Urinary tract tuberculosis**

**Section summary**

Urinary tract TB is essentially a renal parenchymatous disease. It is produced as a result of dissemination through the bloodstream from a distant focus, which is generally pulmonary. It is therefore a bilateral disease, although it manifests as a localised one. In almost all cases there is a cured or active pulmonary lesion. It manifests when the lesion ulcerates a calyx or the renal pelvis, producing bacteriuria, pyuria, and abnormalities that can be detected radiographically; it is in this way that the rest of the urinary tract is most often affected.

This disease can be diagnosed with certainty only when the presence of *M. tuberculosis* is demonstrated in urine cultures. Diagnosis cannot be certain with the detection of the typical lesions in the intravenous urography, or with the detection of acid-alcohol—resistant bacilli in the urine—these merely suggest the disease. Radiological findings may be very useful in diagnosis, especially those provided by intravenous urography. Treatment is the same as that for pulmonary TB, and surgical intervention should be evaluated in the case of complications or sequelae.
Urinary tract TB is essentially a renal parenchymatous disease. It manifests when the lesion ulcerates a calyx or the renal pelvis, producing bacteriuria, pyuria, and abnormalities that can be detected radiographically. The absolute requirement for diagnosis is demonstration of urine cultures, and not the detection of the typical lesions in the intravenous urography, nor the detection of acid-alcohol—resistant bacilli in the urine—these merely suggest the diagnosis.

The presence of *M. tuberculosis* in renal TB is the result of dissemination through the bloodstream from a distant focus, which is generally pulmonary. It is therefore a bilateral disease, although it is manifested as a localised one. In almost all cases, there is a cured or quiescent pulmonary lesion. The only visible lesion is often a small scar or a lesion that has been forgotten by the patient, and it is not unusual for long periods of time to elapse between the pulmonary infection and urinary manifestation. Dissemination to the kidney from a contiguous lumbar lesion is rare, and secondary involvement in various parts of the organism may coincide. Secondary to the release of emboli through the bloodstream, multiple foci in glomerular tubular capillaries appear, the majority of which will spontaneously lead to a cure, depending on the number and virulence of the bacteria and host resistance. When cure is not spontaneous, necrosis occurs and the bacteria pass into the tubules and can be detected in urine.

The first radiographically visible lesion will be ulcerous cavitary papillitis resulting from the necrosis and coalescence of the tubercles. Found on the narrow part of the loop of Henle, they will affect the calyceal wall, normally at the end of the papilla. There may be one or several lesions that may be unilateral or bilateral and may progress to produce a calyceal deformity where the outline disappears and a cavity is formed. The calyces become connected to each other through a progression of cavities or through fistulous trajectories. The disease may evolve from a mucus involvement of the other calyces, urethra, or bladder. The multiple granulomatous lesions are accompanied by ulcerations, fibrosis, and stenosis. In areas where there is physiological narrowing of the urinary tract, such as the calyceal infundibula and the ureteropyelic and ureterovesical junction, these stenoses will produce caliectasis, hydrophronesis, and urethrohydronephrosis, with secondary destruction of the renal parenchyma. Curing these lesions will further aggravate the fibrosis and stenosis, possibly amputating part of a calyceal group or the whole kidney, which will not be visible with intravenous urography (partial and/or total autoamputation, or autonephrectomy). Apart from fibrosis and stenosis, the cure is characterised by the existence of calcic deposits. Calcifications may vary in density and extension.
For diagnosis, it is necessary to take three urine samples over 3 consecutive days, preferably early in the morning when the patient wakes up. Because other environmental mycobacteria are present in the urethra and glans and thus may also be isolated, smear microscopy is non-specific. For this reason, a culture of the urine sample is essential for a definite diagnosis. However, this does not mean that it is not necessary to carry out smear microscopy of the sample. Despite its non-specificity, the fact remains that a request for this technique indicates a suspicion of TB of the genitourinary tract. If this is the case, a positive smear microscopy can be of great value as it increases the positive predictive value of the technique. It will be of less value if the positive smear microscopy is obtained from an asymptomatic patient or a patient with symptoms that are not suggestive of TB; in such cases, a request for microscopic study is not indicated.

It is necessary to highlight the value of imaging techniques in guiding the diagnosis of genitourinary TB, especially when the lesions that suggest this disease are shown on intravenous urography. A normal finding with intravenous urography does not rule out the diagnosis. Further, renal TB causes no radiographic pathognomonic changes. Although it frequently produces very characteristic radiographic abnormalities, it is important to remember that all chronic inflammatory lesions may conceal non-tuberculous pyelonephritis. The imaging study should begin with a simple abdominal radiograph, which may show: 1) associated skeletal lesions; 2) calcifications in other areas—such as hepatic or splenic granulomas, or calcified mesenteric adenopathies; or 3) renal or genitourinary calcifications. Tuberculous calcifications are more tenuous and more poorly defined than lithiasic calcifications, and may differ in size. They are also more cortical in location, although they may coexist with calculi. When these are generalised, it is known as nephrocalcinosis (Figure 54). Apart from the kidney, the urethra may calcify, although this is much less common, and calcifications may also be found in the prostate, seminal vesicles, and other such sites.

When there is reasonable doubt about whether the symptoms are caused by TB, intravenous urography is indicated. The earliest urographic sign is in the calyxes, and caliectasis is the most common early finding. Sometimes there is minimal erosion of the point of the calyx (ulcerous cavitary papillitis) or very slight calyceal irregularities, which is quite often very difficult to distinguish from pyelosinus reflux. As the infection progresses the caliectases increase, and it is possible to visualise cavities that are at times connected by fistulous trajectories (Figure 55). The process of cicatrization and fibrosis is the most common finding, with infundibular stenosis
Figure 54. Simple radiograph of the abdomen showing a small right kidney, with cavities and calcic-deposits (nephro-calcinosis). Autonephrectomy.

Figure 55. Intravenous urography demonstrating a small cavity in the upper left calyceal group. Renal TB was confirmed by urine culture.
Figure 56. Intravenous urography showing infundibular stenosis of the upper calyceal group, as well as a large tuberculous cavity. Diagnosis of renal TB was made by smear microscopy and urine culture.

Figure 57. Intravenous urography showing a typical retraction of the renal pelvis, with caliectasis caused by chronic tuberculous pyelone-phritis. Diagnosis of renal TB was made by smear microscopy and urine culture.
(Figure 56) that may partly isolate part of the collecting system or a calyx. It is sometimes difficult to distinguish a cavity (Figure 56) from a dilated calyx.

Retractions in the renal pelvis are accompanied by characteristic deformities (Figure 57) and, in the urethra, by areas of stenosis (Figure 58), which are more commonly found in areas that are physiologically narrowed (intersection of the bladder trigone iliac vessels and the ureteropelvic junction). Non-tuberculous pyelonephritis and non-specific stenosis may produce similar findings.

The lesions in the urethra are due to renal or vesicle TB, and the earliest changes to take place are dilatations and irregularities of the wall, indicating the existence of ulcerations and oedemas. Afterwards, the urethra loses elasticity and evolves towards fibrosis and stenosis, which will be more pronounced in physiologically narrowed areas (Figure 58). There may be one or multiple stenoses, which may be long or short and may alternate with other areas of dilatation and stenosis, giving the urethra the appearance of a rosary.

Bladder involvement is most commonly manifested as retraction, a decrease in capacity, showing smaller bladders that sometimes lead to a vesicular urethral reflux and cause an ascending infection. The evolution of the disease towards fibrosis and stenosis, and the actual effect of chemotherapy, will further aggravate retraction (Figure 59).

Ultrasounds can be particularly useful for evaluating a kidney that has been deemed functionally annulled with intravenous urography, and may serve as a guide for aspiration puncture when the diagnosis is uncertain. Computed tomography may help to delimit the extension of the renal or extrarenal abscesses; however, its use is not indicated in uncomplicated cases as intravenous urography provides sufficient support for a diagnosis of renal TB.

The genitals may also become affected, although this is extremely uncommon. Any organ may be affected in male subjects, although perhaps the most common presentation is epididymis TB (Figure 60). Likewise, any organ may be affected in female subjects; the most commonly affected areas are the annexes (tuberculous annexitis), which causes an inflammation of the fallopian tubes and frequently causes sterility. One curious point worth mentioning is that genital TB can also be caused as a result of direct inoculation during sexual intercourse.

Treatment is the same as for pulmonary TB, and surgical intervention should be evaluated in the event of complications or sequelae.
Figure 58. Ascending pyelography showing the pronounced destruction and deformity of the collecting systems and renal pelvis, with dense shadowy areas of caseum and contrast in the cavities. Cortical atrophy and urethral stenosis are also seen. Advanced renal and urethral TB was confirmed by smear microscopy and urine culture.

Figure 59. Intravenous urography showing a vesicle retraction and deformity, with a trigone filling defect as a result of the affected urethra. TB of the bladder was confirmed by urine culture.
Inflamed right testicle with internal suppuration. Diagnosis of epididymis TB was made by culture of a sample obtained through an aspiration puncture using a thin needle. The patient had advanced pulmonary TB.

Bone and joint tuberculosis

Section summary

Bone TB is a secondary condition that results when a pulmonary focus disseminates through the bloodstream. However, evidence of an active pulmonary lesion is 30% to 50%. The bone lesions result when the bacilli reach the bone marrow, which represents approximately 20% of all cases of extrapulmonary TB.

Bone TB more commonly involves the vertebrae, especially the lower part of the dorsal and lumbar column, in 50% of cases. Bone TB may affect the epiphysis, metaphysis, and diaphysis, although it more commonly affects the first two, secondary to affecting the joints. The lesion is typically destructive. It evolves slowly and is eccentric, and there is a lack of reactivity of the adjacent bone, although it may sometimes be accompanied by a periostic reaction and soft tissue mass (cold abscess).

The presence of multiple lytic lesions in an oligo-asymptomatic patient, with no demonstrable reactive changes, should lead to a suspicion of TB.
Depending on the site affected, there are various types of vertebral TB: disc, paradiscal, somatic, ligamentous, and atypical. Joint lesions are the most common after vertebral ones, and the larger joints are more likely to be affected. Involvement is usually monoarticular, affecting only one joint and, in descending order of frequency, involving the hip, knee, ankle, shoulder, wrist, and elbow. The earliest radiographic sign of joint TB is severe periarticular demineralisation. Joint TB can only be diagnosed with certainty through a culture, which makes it necessary to obtain biopsy samples from the area affected. Data supporting the diagnosis can also be obtained from radiographic studies (simple radiology, techniques using isotopes, computed tomography, and magnetic resonance imaging). Treatment is the same as that used in pulmonary TB, although some groups recommend that treatment be prolonged for up to 9 to 12 months.

Bone TB is a secondary condition that results when a pulmonary focus disseminates through the bloodstream. There is evidence of an active pulmonary lesion in 30% to 50% of cases. The bone lesions result when the bacilli reach the bone marrow, which represents approximately 20% of cases of extrapulmonary TB. It more commonly (> 50%) involves the vertebrae (Figure 61). Bone TB may affect the epiphysis, metaphysis, and diaphysis (Figures 62 and 63), although it more commonly affects the first two, secondary to affecting the joints. The lesion is typically destructive, evolves slowly, and is eccentric. There is a lack of reactivity of the adjacent bone, although it may sometimes be accompanied by a periostic reaction and soft tissue mass (cold abscess). The lesion may sometimes be diaphyseal, with a very characteristic appearance when it affects the short bones of the hands and feet, widening the medullary channel of the affected bone, a lesion known as spina ventosa. When bone TB is disseminated and destructive, and accompanied by little reactive sclerosis, it is known as TB of the cystic bone (Figures 63 and 64). The presence of multiple lytic lesions in an oligo-asymptomatic patient with no demonstrable reactive changes should lead to suspicion of TB. Just one lytic lesion (Figures 63 and 64) may be similar in appearance to an osteosarcoma. In fact, the lesions caused by bone TB are similar to those caused by pyogenic osteomyelitis, but with less destruction and reactivity of the adjacent bone.

As explained earlier, vertebral TB is the most common form of extrapulmonary TB, and more frequently involves the lower part of the dorsal and lumbar columns (Figure 61). This condition has been known as Pott’s disease for over 200 years. Depending on the site involved, there are various
types of vertebral TB: disc, paradiscal, somatic, ligamentous, and atypical. The purely disc form possibly results from dissemination by contiguity from a vertebral focus that is not visible on a radiograph. The paradiscal form is the most common and is manifested by involvement of the discs, vertebral plates, and paravertebral soft tissue mass (Figure 61). Its evolution is characterised by a loss of bone density, which leads to early hyperaemia, followed by marginal erosion in the phase of granuloma formation and a slow progression towards final bone destruction (Figure 61). The intervertebral space is maintained for a long time in the case of TB, in contrast with pyogenic infection. This difference can be of great importance in a differential diagnosis, although it is almost always better to differentiate between these two processes using clinical as opposed to radiographic data. The somatic form, which is more common among children, is presented as a vertebral osteomyelitis that leads to collapse of the body, occasionally accompanied by neurological lesions. The atypical forms are those that affect the neural arch and that lead to serious complications if the canal is infected. In these

Figure 61. Lateral radiograph of the lumbar column showing discitis of L4-L5. Diagnosis of TB was through anatomic-pathological study and culture of a biopsy specimen from the area.
Figure 62. Simple shoulder radiograph showing severe joint involvement after evolving over 2 years, with destruction of the humerus head. Diagnosis of TB was through anatomic-pathological study and culture of a biopsy specimen from the area.

Figure 63. Simple tomographic scan of the right shoulder. Erosive epiphyseal involvement with cavitation was observed. TB was confirmed by anatomic-pathological study and culture of a biopsy specimen from the area.
instances, computed tomography and nuclear magnetic resonance imaging allow a more complete evaluation, both with regards to the extension of the lesions and the study of other complications such as the migration of cold abscesses.

Vertebral TB is accompanied by soft tissue mass, normally symmetrically arranged in the paravertebral region. These are the so-called “cold abscesses”, which later end up calcifying. Computed tomography and nuclear magnetic resonance imaging can be valuable methods for studying these lesions. They allow early detection and better evaluation of their characteristics, and also serve as a guide for percutaneous puncture in cases where diagnosis is uncertain.

When the vertebrae are affected, it may not be certain if vertebral collapse was due to a neoplastic or an infectious cause. The combination of loss of height in the disc and badly defined contiguous vertebrae are very important signs of infectious aetiology, since a reduction in height of a disc is an exceptional occurrence in neoplastic lesions. The presence of paravertebral mass, in the phase when it has not yet calcified, is a finding reflecting both a neoplastic and an infectious process.
Joint lesions are the most common after vertebral ones, and the larger joints are more likely to be affected. Usually only one joint is affected. In descending order of frequency, the joints involved are the hip, knee, ankle, shoulder, wrist, and elbow.

Joint TB has characteristics that differentiate it from the pyogenic conditions. In pyogenic arthritis the inflammatory exudate has many more proteolytic enzymes, which cause significant destruction, unlike what happens in tuberculous arthritis. The location of the cartilaginous destruction is also different, given that pyogen occurs in cartilage in apposition, which supports weight, whereas TB generally affects free surfaces. The exceptions to this are the hip, ankle, and metacarpophalangeal joints, which generally show profuse damage as they have little free surface. Another difference is progression time, which is quick in pyogenic arthritis but slow in the case of TB (Figure 62).

The earliest radiographic sign of joint TB is severe periarticular demineralisation. This is believed to be related to local hyperaemia, disuse, and the action of the bacterial toxins, although its origin is not yet understood. Initially, periarticular blurring may also occur, which is why it is important to compare radiographs so that this sign can be detected early on. Tumefaction of the soft tissues and changes in the bone are observed later, appearing in the articular margins that do not support weight (Figure 62). Joint involvement may present as synovitis or as osteoarthritis, with periarticular tumefaction in cases of synovitis with osteoporosis (cold tumour). The formation of granulomas in the synovial membrane will progress to osseous invasion with marginal erosions, which, in the case of the knee, may occur on both sides of the joint (kissing lesions). This type of lesion may lead to destruction of the joint (Figure 62) and calcification of the soft tissue; differential diagnosis will concern algodystrophy or other granulomatous involvement. In children, any cause of chronic synovitis that can also produce juxtaarticular atrophy or synovial hypertrophy, and an increase in epiphysias, should be noted. In adults, joint TB must be differentiated from primary rheumatoid arthritis, although joint TB is generally polyarticular and affects the small joints. Differentiation can be difficult when the condition begins as monoarticular, affecting a medium-sized joint. In such cases it is important to evaluate the critical and analytical criteria.

In order to diagnose joint TB with certainty, it is necessary to isolate colonies of *M. tuberculosis* in culture. Thus, biopsy samples should be obtained from the affected area and processed for microbiological and anatomic-pathological study. Obtaining valid biopsy samples may determine
whether major surgical intervention is needed, since the suspected diagnosis, radiological findings, and endemic rate in the region may not point to the need for surgery. If other possible diseases can be reasonably ruled out, especially those of neoplastic origin, antituberculous treatment may be indicated in low- and middle-income countries and the disease can be followed to see how it evolves. For this reason, imaging techniques can play a very important role in these types of conditions. These methods may include:

1. **Simple radiology.** This is useful for detecting alterations at an early stage and to evaluate the effects of the therapy. The radiographic signs, which have already been covered, include tumefaction or blurring of the soft tissue, juxtaarticular osteoporosis, marginal erosions in the free surfaces, a decrease in space, and, at times, joint destruction (Figure 62) with calcification of the soft tissue.

2. **Techniques using isotopes.** This estimates the physiological activity in the bones and joints, detecting small increases and decreases. Findings are non-specific and thus must be complemented with other methods in order to characterise the abnormal areas. Scanning with technetium will yield signs of involvement early on in the initial phases with a normal radiograph. In addition, it provides information on the whole skeleton. Scanning with gallium, which is sensitive for the detection of inflammation, is useful in detecting early cellulitis. A decrease in the activity of gallium is a good indicator of follow-up with regards to response to therapy, as well as of follow-up to discern the presence of chronic osteomyelitis or its reactivation.

3. **Computed tomography.** This makes it possible to discriminate between contiguous structures based on slight differences in density. The method provides information on the extension of the process, the characteristics of the lesion, and the identification and extension of the extraarticular abscesses. It also guides percutaneous puncture when diagnosis is uncertain.

4. **Magnetic resonance imaging.** Like computed tomography, this method provides spatial resolution, showing better resolution in the contrast of the soft tissue. No contrast injection is required and it is more sensitive than computed tomography when detecting abnormalities, although this does not mean that it has higher specificity. It provides a more precise anatomic delineation of all the structures in the column.

Treatment is the same as that used in pulmonary TB, although some groups recommend that treatment be prolonged for up to 9 to 12 months—a recommendation that, however, has not been shown to be associated with
greater benefit. Nevertheless, depending on the site affected, surgical interventions are quite often necessary, especially to correct deformities or other sequelae.

**Peritoneal and digestive tract tuberculosis**

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| Digestive tract TB can be caused via four mechanisms: 1) by swallowing bacilli when drinking milk from infected cows, or (if infected) by swallowing one’s own sputum, thus affecting the mucous membranes and mesenteric lymph nodes; 2) by dissemination through the bloodstream; 3) by dissemination through the lymph vessels; and 4) by contiguity.  

Intestinal TB can appear in many forms: ulcerative, hypertrophic, or with ileal colic involvement (the ileum and colon are affected in 70% to 90% of cases). During the initial phases, there may be spasms and accelerated transit, followed by thickening of the ileocaecal valve, which appears as a mass in the caecum. The valve is distorted as a result of the ulceration and fibrosis and the ileum narrows.

A gastric or duodenal location is extremely rare and has no specific radiological characteristics. It may appear as an ulcer, or like a carcinoma if the hypertrophic form predominates. Oesophageal involvement is even more rare and also has no specific radiological signs, appearing as an ulceration, area of spasm or adherences, or mediastinal lymph nodes.

Peritoneal TB constitutes two thirds of cases of abdominal TB, with the peritoneum as the primary site in 35% to 58% of patients. Secondary involvement may occur through direct extension (rupture of a lymph node or perforation of the intestinal tract), by dissemination through the bloodstream, or through the lymph vessels. There are three types of tuberculous peritonitis: wet, dry, and fibrotic. The symptoms are non-specific and the most common finding is ascites, with a high protein content and leucocytosis with a predominance of lymphocytes. The culture proves positive in 50% of cases. The determination of ADA in the peritoneal fluid can be very helpful in this case.

Diagnosis should be confirmed by a culture, although this will frequently entail aggressive diagnostic attitudes, which may not be justified in low- and middle-income countries. Treatment is the same as for pulmonary TB.

Owing to the pasteurisation of milk and an improved control of pulmonary TB in developed countries, the incidence of peritoneal and digestive tract TB has decreased considerably, representing 11% to 13% all cases of
extrapulmonary TB. Before this, 50% to 90% of patients with pulmonary TB suffered a gastrointestinal infection. The incidence in poorer countries is not known. The microorganism that is frequently involved is *M. bovis*.

This form of extrapulmonary TB can be caused through four mechanisms: 1) by swallowing bacilli when drinking milk from infected cows, or (if infected) by swallowing one’s own sputum, thus affecting the mucous membranes and mesenteric lymph nodes; 2) by dissemination through the bloodstream; 3) by dissemination through the lymph vessels; and 4) by contiguity. The presence of the bacilli at a mucous membrane will cause acute localised inflammation of the lymph tissue of the submucosa. After 2 to 3 weeks, tubercles are formed with epithelial cells and lymphocytes, after which the tubercles undergo gas necrosis and fibrous cicatrisation.

There are several types of intestinal TB:

1. **Ulcerative form.** This is characterised by elongated ulcers perpendicular to the large intestinal axis, which may have irregular edges and have a pronounced spasm of the loop affected during the acute phase, leading to functional stenosis (Figure 65).

2. **Hypertrophic form.** This is characterised by a pronounced inflammatory fibroblastic reaction. An abdominal mass can frequently be felt, with severe associated mesenteric involvement. The surface of the mucous membrane may have a multi-nodular pattern or be a large mass that cannot be distinguished from a tumour. There may be mixed ulcer-hypertrophic forms with cobbled markings or a large abdominal mass. The areas most frequently affected are the proximal and distal colon, and the ileocaecal region is the most typical location (Figure 66). Involvement of the oesophagus (Figure 67), stomach, duodenum, and rectum is extremely rare. The most frequent complication is obstruction (12-69%). Fistulisation and haemorrhage are less common. Perforation is also very infrequent (< 10%), probably due to thickening of the intestinal wall and the mesentery, which produces the disease.

3. **Ileal-colic involvement.** The ileocaecal location is the most frequent involved, constituting 70% to 90% of cases (Figure 66). In the early phases, spasms and accelerated transit are observed, followed by thickening of the ileocaecal valve, with the appearance of a mass in the caecum. The valve is distorted as a result of the ulceration and fibrosis, and the ileum narrows (Figure 66). More advanced studies may show retraction with a pronounced shortening of the caecum. A fibrotic ileum terminus ending in a retracted caecum with an incompetent ileocaecal valve is
classically known as the Stierlin’s sign. Other intestinal diseases may be
similar in appearance, and at times differentiation can be difficult, espe-
cially in the case of Crohn’s disease and amebiasis. In the colon the dis-
ease is manifested as an ulcerated segmented lesion, with spasms and
rigidity of the wall, which may be accompanied by a mesenteric mass
and, at times, fistulisation (Figure 65).
A gastric or duodenal location is extremely rare and has no specific
radiological characteristics. It may appear as an ulcer, or as a carcinoma, if
the hypertrophic form predominates.
Oesophageal involvement (Figure 67) is even more rare and also has
no specific radiological signs. It sometimes appears as an ulceration, area of
spasm or adherences, or mediastinal lymph nodes. Stenosis and fistulous
tracts may be produced as a result of the penetration of the contents of a
mediastinal adenopathy in the oesophageal lumen. This is a very unusual
location. The differential diagnosis should include bronchogenic or metas-
tatic carcinoma with secondary infiltration of the oesophagus; neoplasia of
the oesophagus; and, rarely, Crohn’s disease. In cases where the oesophagus
is involved, computed tomography will be useful for observing the extralum-
inal extension.
Peritoneal TB constitutes two thirds of cases of abdominal TB, with the
peritoneum as the primary site in 35% to 58% of patients. Secondary
involvement may occur through direct extension (rupture of a lymph node
or perforation of the intestinal tract), by dissemination through the blood-
stream, or through the lymph vessels. There are three types of tuberculous
peritonitis: 1) the wet type, with free or encapsulated ascites; 2) the dry type,
with caseous nodules (plastic peritonitis); and 3) the fibrotic type, fixed with
an abdominal mass.
The symptoms are non-specific and the most common finding is ascites,
with a high protein content and leucocytosis with a predominance of lym-
phocytes. The culture proves positive in 50% of cases. Ascites may be
detected through clinical exploration, using ultrasound or computed tomog-
raphy, where highly attenuated peritoneal fluid can generally be seen. Like-
wise, involvement of the mesentery and epiploon may be observed,
appearing to have a higher density, or as a solid mass replacing the normal
epiploon (omental cake). The differential diagnosis should include bacterial
peritonitis, peritoneal carcinomatosis, and mesothelioma.
To diagnose peritoneal TB and TB of the digestive system with cer-
tainty, it is necessary to isolate colonies of *M. tuberculosis* in a culture. This
means that it is frequently necessary to obtain biopsy samples from the
Figure 65. Opaque enema. TB of the colon, ulcerative type, with functional stenosis. Diagnosis was made by anatomic-pathological study and culture of a biopsy specimen of the area, obtained using a colonoscope.

Figure 66. Opaque enema. Ileocaecal TB. Ileal stenosis with mesenteric thickening and retraction of the caecum. Diagnosis was made by anatomic-pathological study and culture of a biopsy specimen of the area, obtained using a colonoscope.
affected area, which must be processed for microbiological and anatomic-pathological study. Obtaining suitable biopsy samples may determine whether or not major surgical intervention is needed, since surgery may or may not be indicated by the suspected diagnosis, the radiological findings, and the endemic rate in the region. If other possible diseases can be reasonably ruled out, especially those of neoplastic origin, in low- and middle-income countries it may be advisable to start antituberculous treatment and see how this evolves. For this reason, imaging techniques can play a very important role in these types of extrapulmonary involvement. The determination of ADA in the peritoneal fluid can be very helpful, since detection of ADA very often obviates the need for more aggressive explorations. In addition, as these extrapulmonary types of TB are paucibacillary forms, genetic amplification techniques (e.g., PCR) may be very useful in the diagnosis (see Chapter 8).

Treatment is the same as that used in pulmonary TB, although some groups recommend that treatment be prolonged for up to 9 to 12 months.
This recommendation, however, has not been shown to be any more beneficial than the standard regimen. Depending on the site involved, surgical intervention may be necessary, especially in the case of intestinal obstruction. It is necessary to evaluate the rest of the cases carefully as this type of surgery may lead to even more adherences.

Tracheobronchial and upper airways tuberculosis

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| TB of the trachea and large bronchi in children is frequently a complication of the primary disease. It may be associated with mediastinal adenopathies. Endobronchial involvement is the result of rupturing of caseous material in the bronchial wall, or of dissemination through the lymph vessels throughout the bronchial tree producing ulcerations in the mucous membrane. This form is known as gangliobronchial TB. Endobronchial involvement occurring via the direct implantation of tuberculous bacilli from active parenchymatous lesions, which are transmitted through the air, is most common in adults. The most common symptoms, apart from the general TB symptoms, are a persistent cough and possible stridor. The epiglottis, larynx, and pharynx are frequently affected and are usually an extension of pulmonary TB. Clinical manifestations include hoarseness, earache, pain on swallowing, and ulcerations on the tongue.

It is difficult to know how prevalent these types of TB are since a smear microscopy and/or positive culture are the principal diagnostic tests used in all cases. Nevertheless, in the case of pulmonary TB, these results will aid in the diagnosis of the disease in the vast majority of cases, considering that the upper airways, trachea, or large bronchi may also be affected. |

The prevalence of tuberculous involvement of the trachea and large bronchi is currently unknown. Before chemotherapy, it was traditionally considered a complication of cavitary TB and was a fairly common presentation. Since the arrival of effective antituberculous drug treatment, these forms of extrapulmonary TB are more likely to be considered a rarity, although there is some disagreement regarding this point. Various mechanisms are involved in these forms of TB.

In children, this is frequently a complication of primary TB. It may be associated with large mediastinal adenopathies, and endobronchial involvement is the result of rupturing of caseous material in the bronchial wall, or of dissemination through the lymph vessels throughout the bronchial tree, which produces ulcerations in the mucous membrane. This form is known as gangliobronchial TB. These adenopathies do not only perforate the
bronchus but may also compress it. For various reasons, residual stenotic lesions may form in the airway, possibly leading to future repeated infections. In these cases, early diagnosis is of critical importance as a high percentage of cases will need aggressive treatment if complications are to be avoided.

Endobronchial involvement via direct implantation of tuberculous bacilli from active parenchymatous lesions, which are transmitted through the air, is the most common cause of infection in adults, and less so in children. The most common symptoms, apart from the general TB symptoms, are a persistent cough and possible stridor.

The epiglottis, larynx, and pharynx are frequently affected, usually as an extension of pulmonary TB. Clinical manifestations include hoarseness, earache, pain on swallowing, and ulcerations on the tongue. This type of TB must be differentiated from cancer of the larynx, although the latter condition is rarely painful.

It is difficult to know how prevalent these forms of TB are as smear microscopy and/or positive culture are the principal diagnostic tests used in all of these cases. It is generally accepted that the incidence of bronchial TB is increasing in the HIV-infected population, which may explain some cases in which a smear-positive result and a normal chest radiograph have been observed. In the case of pulmonary TB, these results will be true in the vast majority of cases and may lead to a diagnosis of the disease, while considering the possibility that the upper airways, trachea, or large bronchi may also be affected. For this reason, in order to determine if there is extrapulmonary involvement, it is necessary to use endoscopic techniques, such as laryngoscopy and bronchoscopy, which are capable of locating the lesions and serving as a guide for a biopsy to confirm the diagnosis. In any event, treatment and cure are the same as with pulmonary TB, although surgical intervention is sometimes necessary in the case of gangliobronchial TB in children.

Cerebral and meningeal tuberculosis

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<td>This type of TB is one of the most serious forms; therefore, early diagnosis and treatment are essential. The bacilli may enter the subarachnoidal space, causing inflammation of the meninges, formation of a mass at the base of the brain, or inflammation and reduction of the diameter of the arteries, which can lead to brain damage. General manifestations include a decline that takes place over the course of 2 to 8 weeks, malaise, irritability, change in behaviour, anorexia, weight loss, and a slight increase in temperature. A lumbar puncture is necessary for diagnosis. The sensitivity of smear microscopy (&lt; 10%) and culture (&lt; 50%)</td>
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in cerebrospinal fluid is very low, since cerebrospinal fluid generally has very few cells, low glucose levels (which is a prognostic factor), a predominance of lymphocytes, and ADA levels over 9 international units. Treatment is the same as that used for pulmonary TB, although some scientific societies advocate prolonging the treatment for up to 9 to 12 months, owing to the difficult diffusion of drugs in the meninges.

This type of TB is one of the most serious; therefore, early diagnosis and treatment are essential. In fact, it is one of the few times that it is imperative to take urgent action and provide guidelines for the treatment when there is the slightest suspicion, chiefly because of the low performance of the available diagnostic techniques. The bacilli may enter the subarachnoidal space, causing inflammation of the meninges, formation of a mass or tuberculoma at the base of the brain (Figure 68), or inflammation and reduction of the diameter of the arteries, which can lead to brain damage.

Figure 68. Computed tomographic scan of the cranium showing a large cerebral mass on the right. Cerebral tuberculoma was diagnosed by anatomic-pathological study of a biopsy sample.
General manifestations include a general decline occurring over the course of 2 to 8 weeks, malaise, irritability, change in behaviour, anorexia, weight loss, and a slight increase in temperature. Symptoms then progress to include headache, vomiting, and cervical tension, quickly leading to a loss of consciousness. It is important to be able to recognise the different stages of this progressive clinical manifestation, since the prognosis is different for each stage. Thus, increased awareness of the clinical symptoms is absolutely essential in order to obtain a diagnosis during the earliest phases of the disease. To this end, the following three stages have been described:

**Stage I.** Manifestations are mostly systemic.
- The patient is conscious and lucid.
- There are meningeal symptoms but no neurological signs.

**Stage II.** The patient has time-space disorientation.
- Confusion is observed.
- There are neurological signs of endocranial hypertension.

**Stage III.** The patient finds it very difficult to remain conscious.
- Profound stupor, delirium, or coma may occur.
- Hemiplegia or paraplegia may occur.

To diagnose the disease, it is necessary to carry out a lumbar puncture and obtain cerebrospinal fluid. However, cerebrospinal fluid contains very few bacilli, and as such the sensitivity of smear microscopy (< 10%) and the culture (< 50%) is very low. The disease can be suspected if the clinical manifestation includes cerebrospinal fluid with very few cells, high protein levels, and low glucose levels, which is a prognostic factor, and a predominance of lymphocytes. In addition, the determination of ADA in cerebrospinal fluid can be very helpful as it is highly sensitive and specific (> 90%). The cut-off point to achieve these high levels of sensitivity and specificity will be established by the laboratory carrying out the test, but it is generally accepted that more than 9 international units is highly suggestive of TB. In addition, as they are paucibacillary forms of TB, genetic amplification techniques such as PCR may be of great help in the diagnosis (see Chapter 6).

The patient will die if treatment is not started immediately. With a correct diagnosis and effective treatment, there is a higher chance of recovering without incurring any permanent, serious brain damage. A delay in diagnosis will severely affect prognosis, with the possibility of hydrocephalus. Treatment is the same as for pulmonary TB, although some scientific societies advocate prolonging the treatment to 9 to 12 months because of the difficult diffusion of drugs in the meninges. The drug that best passes through the
blood-brain barrier is pyrazinamide, although isoniazid, rifampicin, ethambutol, and streptomycin also have good capacity, especially if the meninges are inflamed.

**Other locations of tuberculosis**

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| As already explained, TB can affect any organ or tissue. Nevertheless, many locations of extrapulmonary TB are extremely uncommon, even anecdotal.  
  
  *M. tuberculosis* can affect both the female and male genital tracts if disseminated through the blood, or through the urinary tract. In women, it is frequently manifested as abdominal or pelvic pain, an abdominal mass, infertility, or ectopic pregnancy. Men with genital TB will often present with a mass in the testicular region.  
  
  Adrenal TB will always enter in the differential diagnosis of adrenal insufficiency. General manifestations include weakness, fatigue, nausea, vomiting, and pigmentation of the skin.  
  
  The clinical presentation of cutaneous TB is very variable, but there will always be non-pathognomonic lesions, which may range from small papules and erythemas to large tuberculomas. TB should always be suspected when chronic, painless cutaneous lesions are observed.  
  
  *TB of the skeletal muscle* is exceptionally rare and is almost always a result of dissemination through the bloodstream. *TB of the diaphragm* is even more rare, which, despite being a well-vascularised muscle, is more frequently affected via invasion by contiguity from the pleura and subpleural pulmonary foci. |

**Genital tuberculosis**

*M. tuberculosis* may also reach the female and male genital tracts if disseminated through the blood or through the urinary tract. In women, it frequently manifests as abdominal or pelvic pain, an abdominal mass, infertility, or ectopic pregnancy. Men with genital TB will often present with a mass in the testicular region (Figure 60).

To diagnose this disease, it is frequently necessary to use invasive techniques to obtain biopsy specimens or to perform thin needle aspiration. Ultrasounds can often provide valuable data. Differential diagnoses should include this form of the disease. Treatment is the same as for pulmonary TB.

**Adrenal tuberculosis**

In countries where the disease is highly endemic, TB is the most frequent cause of adrenal insufficiency or Addison’s disease. This frequency is notably
reduced in developed countries. In any event, the disease should be included in the differential diagnosis of adrenal insufficiency. General manifestations include weakness, fatigue, nausea, vomiting, and pigmentation of the skin. One important radiological finding is calcifications in the adrenal region in 20% of cases. The laboratory test, if available, will show low serum sodium levels and high potassium levels. Diagnosis is almost always reached after a biopsy or puncture of the area, and treatment is the same as for pulmonary TB.

**Cutaneous tuberculosis**

As the location is very unusual, this form of TB is frequently not diagnosed. Its clinical presentation is very variable, although there will always be non-pathognomonic lesions, which may range from small papules and erythemas to large tuberculomas. It is necessary to distinguish between nodular erythema—an expression of delayed hypersensitivity produced after a primary infection generally yielding a non-specific biopsy result—and Bazin’s erythema induratum, tuberculids, and other types of cutaneous TB—where the biopsy sample generally does reveal typical lesions, with calcified granuloma. Nodular erythema frequently provides no characteristic data, not even in the biopsy sample, suggesting that diagnosis is made by exclusion. An antituberculous treatment will cure the disease.

TB should always be suspected when chronic, painless cutaneous lesions are observed. Diagnosis will be based on results from a biopsy of the area that is cultured for mycobacteria. Treatment is the same as that for pulmonary TB, although it is important to note that the lesions may evolve very slowly, even when the treatment is correct.

**Tuberculosis of the skeletal muscle and diaphragm**

Skeletal muscle is extremely well irrigated; thus, it is thought to become infected as a result of dissemination through the bloodstream. In some cases though, it may be due to contiguity. Before the availability of chemotherapy, contiguity was fairly common in cases of TB, especially as a result of local dissemination from empyemata necessitatis. At present, TB of the skeletal muscle is exceptionally rare. TB of the diaphragm is even more rare. The diaphragm, despite being a well-vascularised muscle, is more frequently affected through invasion by contiguity from the pleura and subpleural pulmonary foci. It can also occur as a result of dissemination through the bloodstream, although this is less likely. Tuberculous involvement has also been
described in the breast, sub-cutaneous tissue, pericardium, oesophagus, chest wall, retroperitoneum, flank, and even in the groin, hip, and thigh as a result of contiguity and always related to empyema necessitatis. The infrequent involvement of the chest wall by TB, as is the case for the other skeletal muscle locations, is more often related to dissemination through the bloodstream than to direct extension, despite the fact that periostitis in the ribs subadjacent to the areas where pulmonary lesions are caused by TB has been frequently described.

In diagnoses involving these extrapulmonary sites, it is necessary to obtain biopsy samples. In some cases, the anatomic-pathological or microbiological laboratory reports may indicate that it is TB. In any event, treatment and cure are the same as for pulmonary TB.

**Recommended reading**


Chapter 18 - Diseases caused by environmental mycobacteria

Chapter summary
Since it is not mandatory to declare diseases caused by environmental mycobacteria, data regarding their incidence and prevalence must be considered approximate. All of these mycobacteria can be found distributed widely throughout the environment, particularly in the water and ground, which are the principle reservoirs. The prevalence of the disease and the responsible species are found in a wide range of geographic locations, and there has been a considerable increase in the incidence over the last 15 years, most of which have been HIV related.

At present, the concept of “colonisation” is rejected, although there are many clinical manifestations that would be difficult to explain without using this term. However, the considerable limitations of sensitivity tests to antitubercular drugs are unanimously accepted (the majority of these species are resistant to these drugs in vitro), as is the fact that these are only helpful in specific cases and should include macrolides and quinolines.

Treatment will therefore depend on the sensitivity of the mycobacterium towards different drugs. In the case of disease caused by the M. avium complex, currently the most common type described, important progress has been made, especially with the incorporation of clarithromycin and rifabutin in treatment and prophylaxis. Patients with these forms of the disease must be treated in specialised centres by qualified personnel.

One important aspect is how these diseases are managed in low- and middle-income countries, where they are less common and where there is a lack of diagnostic and therapeutic resources. This chapter includes a simple explanation of how these diseases can be correctly handled even in the poorest of countries.

Fifty years ago, a series of clinical manifestations, many of which were similar to tuberculosis (TB) and that were caused by mycobacteria other than M. tuberculosis and M. leprae, began to appear. They were initially classified based on their growth characteristics in vitro and were considered “atypical” mycobacteria for many years, although perhaps a more suitable name for these would be environmental mycobacteria. This group of pathogens has been also known as “non-tuberculous mycobacteria”, “mycobacteria
other than *M. tuberculosis*, “opportunist mycobacteria”, “unclassified mycobacteria”, or “anonymous mycobacteria”. For many years, there was only an occasional, almost anecdotal, description of the diseases caused by these mycobacteria, collectively known as “mycobacteriosis”, the majority of which involved immunodeficiency. Nevertheless, over the last 15 years, this has become quite a common pathology, especially with the start of the HIV epidemic, which has led to an increase in the amount of research on these microorganisms, which in turn has led to the standardisation of diagnostic and therapeutic criteria.

**Epidemiology**

It is not mandatory to declare diseases caused by environmental mycobacteria; therefore, data regarding their incidence and prevalence must be considered approximate. In many cases, these data should be considered in the context of the local laboratories reporting the data, which may involve inconsistent reporting and limited resources for mycobacterial identification. In any event, it has always been accepted that there is a wide geographic variability in the prevalence of the disease and in the species involved. Therefore, the frequency with which each species is isolated varies from one part of the world to another, and even in the same area, over any one period of time.

The majority of papers published on this group of pathogens cite that the risk factors most commonly associated with these diseases are smoking and an underlying lung pathology, such as chronic obstructive lung disease, silicosis, residual TB, or bronchitis.

There has been a significant increase in the incidence of mycobacteriosis in the majority of developed countries over the last few years, even in children, and this has been related to the following factors:
- An increase in the prevalence of chronic obstructive lung disease.
- Improvements in diagnostic techniques.
- The nature of the microorganisms.
- An increase in the clinical awareness of the disease.
- The description in immunocompromised patients (neoplasias, transplant receivers, and steroid users).
- The HIV epidemic. At present, it is unanimously accepted that HIV has led to a marked increase in the incidence of disease caused by environmental mycobacteria, both in number and in species involved.
The disease caused by the *M. avium* complex is the most common form of mycobacteriosis in AIDS patients, and the risk is closely related to the degree of immunosuppression. It is curious to note, however, that there are hardly any cases of the disseminated type caused by the *M. avium* complex in Africa and in the majority of low-income countries where TB is highly prevalent. This phenomenon is difficult to explain, although it has been speculated that the possible immunity to these environmental mycobacteria could be due to the widespread prevalence of the infection and disease caused by *M. tuberculosis*, as well as to wide-scale BCG vaccination. This last hypothesis is supported by data suggesting that infection by *M. tuberculosis* may protect against infection disseminated by the *M. avium* complex.

Table 25 shows the various species of *Mycobacterium*. These are classified according to their speed of growth, principal reservoir, and capacity to cause disease in humans and animals.

**Epidemiological chain of transmission**

Environmental mycobacteria are widely distributed throughout the environment, fundamentally in water and the ground. In the majority of cases, their reservoir is water. In the case of the *M. avium* complex, it is water taps; in fact, there have even been cases of nosocomial epidemics of the disseminated disease (in AIDS patients) transmitted through hospital taps. *M. kansasii* has been repeatedly isolated in water systems and taps, and *M. xenopi*, which needs temperatures over 28°C to grow, is isolated almost exclusively in hot water or hot water systems, which may lead to intra-hospital cases. *M. marinum* also has a reservoir and is transmitted via salt water, fresh fish, reservoir water, and swimming pools, while fast-growing species such as *M. fortuitum*, *M. chelonae*, and *M. abscessus* can be isolated from the ground and from water, although the most common cause of disease involves nosocomial transmission.

Although some data regarding the pathogenesis of the infection and disease caused by this group of mycobacteria still need to be clarified, several studies suggest that person-to-person transmission is rare, and that the majority of cases are caused by microorganisms distributed in the environment. The most accepted transmission mechanism is the aerosolisation of microorganisms in respiratory tract infections, which are then introduced into the digestive system in the case of lymphadenitis in children and disseminated forms in AIDS patients (colonisation of the digestive tract). Direct inoculation of microorganisms from water and other materials has been observed in patients with soft tissue infections.
Table 25. Classification of the species of the *Mycobacterium* genus, according to reservoir, speed of growth, and pathogenic capacity. Source: reference 15, Ruiz Manzano et al, 1998

<table>
<thead>
<tr>
<th>Slow-growing mycobacteria</th>
<th>Fast-growing mycobacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species whose reservoir is infected mammals</td>
<td>Species with an environmental reservoir</td>
</tr>
<tr>
<td>Pathogens for man:</td>
<td>Associated with human disease:</td>
</tr>
<tr>
<td><em>M. africanaum</em></td>
<td><em>M. abscessus</em></td>
</tr>
<tr>
<td><em>M. bovis</em></td>
<td><em>M. chelonae</em></td>
</tr>
<tr>
<td><em>M. leprae</em></td>
<td><em>M. fortuitum</em></td>
</tr>
<tr>
<td><em>M. tuberculosis</em></td>
<td><em>M. macrogenicum</em></td>
</tr>
<tr>
<td>Pathogens for other animals:</td>
<td>Associated with animal disease:</td>
</tr>
<tr>
<td><em>M. lepraemurium</em></td>
<td><em>M. peregrinum</em></td>
</tr>
<tr>
<td><em>M. microti</em></td>
<td><em>M. porcinum</em></td>
</tr>
<tr>
<td><em>M. paratuberculosis</em></td>
<td></td>
</tr>
<tr>
<td>Species with an environmental reservoir</td>
<td>Never or rarely associated with human disease:</td>
</tr>
<tr>
<td>Associated with human disease:</td>
<td></td>
</tr>
<tr>
<td><em>M. asiaticum</em></td>
<td><em>M. agri</em></td>
</tr>
<tr>
<td><em>M. avium</em></td>
<td><em>M. aichienne</em></td>
</tr>
<tr>
<td><em>M. branderi</em></td>
<td><em>M. alvei</em></td>
</tr>
<tr>
<td><em>M. celatum</em></td>
<td><em>M. aurum</em></td>
</tr>
<tr>
<td><em>M. conspicuum</em></td>
<td><em>M. australafriicanum</em></td>
</tr>
<tr>
<td><em>M. genavense</em></td>
<td><em>M. brumae</em></td>
</tr>
<tr>
<td><em>M. haemophilium</em></td>
<td><em>M. chitae</em></td>
</tr>
<tr>
<td><em>M. interjectum</em></td>
<td><em>M. chlorophenolicum</em></td>
</tr>
<tr>
<td><em>M. intermedium</em></td>
<td><em>M. chubuense</em></td>
</tr>
<tr>
<td><em>M. intracellulare</em></td>
<td><em>M. confluentes</em></td>
</tr>
<tr>
<td><em>M. kansasii</em></td>
<td><em>M. diemhoferi</em></td>
</tr>
<tr>
<td><em>M. malmoense</em></td>
<td><em>M. dubalii</em></td>
</tr>
<tr>
<td><em>M. marinum</em></td>
<td><em>M. fallax</em></td>
</tr>
<tr>
<td><em>M. scrofulaceum</em></td>
<td><em>M. flavescens</em></td>
</tr>
<tr>
<td><em>M. shimodei</em></td>
<td><em>M. godium</em></td>
</tr>
<tr>
<td><em>M. simiae</em></td>
<td><em>M. gilvum</em></td>
</tr>
<tr>
<td><em>M. szulgai</em></td>
<td><em>M. hussiacum</em></td>
</tr>
<tr>
<td><em>M. triplex</em></td>
<td><em>M. holderi</em></td>
</tr>
<tr>
<td><em>M. ulcerans</em></td>
<td><em>M. komossense</em></td>
</tr>
<tr>
<td><em>M. xenopi</em></td>
<td><em>M. madagascariense</em></td>
</tr>
<tr>
<td>Associated with animal disease:</td>
<td><em>M. magertioense</em></td>
</tr>
<tr>
<td><em>M. farcinogenes</em></td>
<td><em>M. moriokaense</em></td>
</tr>
<tr>
<td><em>M. neoaurosum</em></td>
<td><em>M. neoaurosum</em></td>
</tr>
<tr>
<td><em>M. obuense</em></td>
<td></td>
</tr>
<tr>
<td>Never or rarely associated with human disease:</td>
<td></td>
</tr>
<tr>
<td><em>M. parafortuitum</em></td>
<td><em>M. phlei</em></td>
</tr>
<tr>
<td><em>M. cooki</em></td>
<td><em>M. proriferae</em></td>
</tr>
<tr>
<td><em>M. gastrae</em></td>
<td><em>M. pulveris</em></td>
</tr>
<tr>
<td><em>M. gordonae</em></td>
<td><em>M. rhodesiae</em></td>
</tr>
<tr>
<td><em>M. hibernae</em></td>
<td><em>M. senegalense</em></td>
</tr>
<tr>
<td><em>M. lentiflavum</em></td>
<td><em>M. senegmati</em></td>
</tr>
<tr>
<td><em>M. nonchromogenicum</em></td>
<td><em>M. sphagni</em></td>
</tr>
<tr>
<td><em>M. terrae</em></td>
<td><em>M. thermoresistible</em></td>
</tr>
<tr>
<td><em>M. triviale</em></td>
<td><em>M. tokaiense</em></td>
</tr>
</tbody>
</table>
It is still not known if there is a latent period after infection, but the clinical forms of presentation most commonly described have always been pulmonary involvement, lymphadenitis, skin and soft tissue abscesses, and osteomyelitis. The mycobacteria most commonly involved in these clinical manifestations are *M. avium*, *M. intracellulare*, *M. kansasii*, *M. marinum*, *M. fortuitum*, *M. chelonae*, and *M. scrofulaceum*.

The pathogenesis of the infection caused by the *M. avium* complex is still not clearly understood. While in *M. tuberculosis* the disease can be caused through endogenous reactivation or through primary progression after an exogenous infection, depending largely on the degree of immunodeficiency, in the case of *M. avium* the disseminated disease is thought to generally occur through progression of the primary infection. Some results indicate that the *M. avium* complex is acquired after ubiquitous environmental exposure, which is very difficult to prevent.

**Clinical manifestations: diagnostic criteria**

Traditionally, these environmental mycobacteria have been classified according to their growth characteristics and the pigments they produce. A more recent classification is based on the organs affected and the diseases caused (Table 26).

**Table 26.** Classification of environmental mycobacteria isolated in humans, according to organ affected and pathology. Source: reference 13, Medina, 1999

<table>
<thead>
<tr>
<th>Disease</th>
<th>Common species</th>
<th>Geography</th>
<th>Morphology</th>
<th>Unusual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td><em>M. avium</em></td>
<td>Worldwide</td>
<td>Slow growth, non-pigmented</td>
<td><em>M. simiae</em></td>
</tr>
<tr>
<td></td>
<td>complex</td>
<td></td>
<td></td>
<td><em>M. szulgai</em></td>
</tr>
<tr>
<td></td>
<td><em>M. kansasii</em></td>
<td>USA, Europe</td>
<td>Pigmented</td>
<td><em>M. celatum</em></td>
</tr>
<tr>
<td></td>
<td><em>M. abscessus</em></td>
<td>Worldwide, but mostly in USA</td>
<td>Fast growth, non-pigmented</td>
<td><em>M. asiaticum</em></td>
</tr>
<tr>
<td></td>
<td><em>M. xenopi</em></td>
<td>Europe, Canada</td>
<td>Slow growth, pigmented</td>
<td><em>M. shinodel</em></td>
</tr>
<tr>
<td></td>
<td><em>M. malmoense</em></td>
<td>North Europe, England</td>
<td>Slow growth, non-pigmented</td>
<td><em>M. haemophilum</em></td>
</tr>
</tbody>
</table>

**Table 26.** Classification of environmental mycobacteria isolated in humans, according to organ affected and pathology. Source: reference 13, Medina, 1999

<table>
<thead>
<tr>
<th>Disease</th>
<th>Common species</th>
<th>Geography</th>
<th>Morphology</th>
<th>Unusual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenitis</td>
<td><em>M. avium</em></td>
<td>Worldwide</td>
<td>Generally non-pigmented</td>
<td><em>M. fortuitum</em></td>
</tr>
<tr>
<td></td>
<td>complex</td>
<td></td>
<td></td>
<td><em>M. cheloneae</em></td>
</tr>
<tr>
<td></td>
<td><em>M. scrofulaceum</em></td>
<td>Worldwide</td>
<td>Pigmented</td>
<td><em>M. abscessus</em></td>
</tr>
<tr>
<td></td>
<td><em>M. malmoense</em></td>
<td>North Europe, England</td>
<td>Slow growth</td>
<td><em>M. kansasii</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>M. haemophilum</em></td>
</tr>
</tbody>
</table>
Lung involvement

Chronic pulmonary involvement with a variable, non-specific presentation is the most frequently identified clinical manifestation. The most commonly implicated source is *M. avium*, followed by *M. kansasii*, although in patients not suffering from AIDS *M. kansasii* or other species may be involved, depending on geographic variability. There is often an underlying pulmonary pathology (chronic obstructive lung disease, pneumoconiosis, active or residual TB, cystic fibrosis, smoking, or bronchitis), which makes symptoms difficult to interpret.

Radiological findings are also non-specific (Figures 33 to 36), although thinner wall cavities are more often found than in TB, as well as a more tenuous surrounding pulmonary infiltrate. The pleura are usually preserved at the bases, and effusion is rare. For this reason, it is often difficult to differentiate between active TB and disease caused by other mycobacteria in patients not infected with HIV. Occasionally, when a clinical-radiographical manifestation suggests TB and the smear microscopy is positive, TB may be diagnosed in the patient and antituberculous treatment started; however, this will be followed by great surprise when the patient’s responds poorly to therapy and when the report on the culture shows growth of an environmental bacteria, meaning that treatment will have to be modified.

Over the last few years, it has been noted that high-resolution computed tomographic scan of the thorax may help to diagnose disease caused by

---

<table>
<thead>
<tr>
<th>Disease</th>
<th>Common species</th>
<th>Geography</th>
<th>Morphology</th>
<th>Unusual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td><em>M. marinum</em></td>
<td>Worldwide</td>
<td>Photochromogen, low temperatures</td>
<td><em>M. avium</em> complex</td>
</tr>
<tr>
<td></td>
<td><em>M. fortuitum</em></td>
<td>Worldwide, USA</td>
<td>Fast growth, non-pigmented</td>
<td><em>M. kansasii</em></td>
</tr>
<tr>
<td></td>
<td><em>M. chelonae</em></td>
<td>Australia, tropics, USA</td>
<td>Slow growth</td>
<td><em>M. xenopi</em></td>
</tr>
<tr>
<td></td>
<td><em>M. abscessus</em></td>
<td>Africa, Asia</td>
<td></td>
<td><em>M. malmoense</em></td>
</tr>
<tr>
<td></td>
<td><em>M. ulcerans</em></td>
<td></td>
<td></td>
<td><em>M. genavense</em></td>
</tr>
<tr>
<td>Disseminated</td>
<td><em>M. avium</em> complex</td>
<td>Worldwide</td>
<td>HIV cultures, pigmented, photochromogen</td>
<td><em>M. abscessus</em></td>
</tr>
<tr>
<td></td>
<td><em>M. kansasii</em></td>
<td>USA</td>
<td>Non-pigmented</td>
<td><em>M. malmoense</em></td>
</tr>
<tr>
<td></td>
<td><em>M. chelonae</em></td>
<td>USA</td>
<td>Non-pigmented</td>
<td><em>M. genavense</em></td>
</tr>
<tr>
<td></td>
<td><em>M. haemophilum</em></td>
<td>USA, Australia</td>
<td>Requires hemira, low temperatures, and CO₂</td>
<td><em>M. conspicuum</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>M. marinum</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>M. fortuitum</em></td>
</tr>
</tbody>
</table>
M. avium, sometimes revealing the presence of bronchitis and nodules, a syndrome that is more commonly found in older women who do not smoke.

With regards to intradermoreaction tests, there is a wide variety of cross-reactions among the antigens of different species, although at present there are promising studies being carried out to obtain reactants with a higher specificity for the M. avium complex. This information will depend on the geographic variability of the different mycobacteria. They are known as the sensitins of the different species.

That these microorganisms can be found everywhere in nature suggests the possibility of contamination or transitory infections, particularly in patients with underlying pulmonary pathologies and in those whose sputum samples contain very few microorganisms. This type of case has been called colonisation and is characterised by minimum pulmonary infiltrators, stability, with no cavities and with sporadic isolation of the mycobacteria in the sputum. More recent studies have tried to show that colonisation is, in its strictest sense, quite rare. Consequently, the American Thoracic Society has considered it in its latest recommendations on the criteria for the diagnosis of disease caused by these mycobacteria. However, rejection of the concept of colonisation is sometimes difficult to accept, especially in the immunocompetent patient. It is also difficult to accept the disease caused by environmental mycobacteria (meaning prolonged treatment) in healthy individuals or in individuals with previous bronchial or pulmonary complaints, who, although showing no symptoms or signs, have repeatedly positive sputum cultures for some of these species, especially when these species are non-pathogenic, such as M. gordonae. The topic of colonisation will undoubtedly be brought up for further discussion in the future, particularly with regards to immunocompetent patients.

To diagnose lung disease caused by environmental mycobacteria, it is advisable to follow the criteria defined by the American Thoracic Society, which is based on the following clinical, radiological, and bacteriological data:

1. Clinical data:
   i) Compatible symptoms and signs (cough, temperature, weight loss, haemoptysis, dyspnoea) with a deterioration of the clinical state.
   ii) Exclusion of other diseases or treatments of other pathologies that may produce clinical deterioration.

2. Radiological data:
   i) In simple chest radiology:
      – Infiltrators with or without nodules
      – Cavitation
      – Single or multiple nodules
In high-resolution computed tomography of the chest:
- Several small nodules
- Multi-focal bronchiectasis with or without small pulmonary nodules

3. Bacteriological data. Provided that one or more of the following apply:
   i) Provided that at least three samples of sputum or bronchoalveolar lavage can be obtained in 1 year:
      - Three positive cultures and a negative smear microscopy, or
      - Two positive cultures and one positive smear microscopy.
   ii) If unable to obtain sputum, one bronchoalveolar lavage:
      - With a positive culture (2+, 3+, 4+), or
      - Positive culture with a positive smear microscopy (2+, 3+, 4+).
   iii) Biopsy:
      - Any growth in the sample cultures obtained from bronchopulmonary biopsy specimens.
      - Granulomas and/or observation of acid-alcohol—resistant bacilli in a pulmonary biopsy specimen with one or more positive cultures of sputum or bronchoalveolar lavage.
      - Any growth obtained from sterile extrapulmonary samples.

   The same criteria apply for immunosuppressed patients, although in this case a positive culture showing growth of 1+ or more is considered diagnostic.

**Peripheral lymphadenitis**

Another clinical manifestation frequently caused by these mycobacteria is peripheral lymphadenitis, which is most frequently found in children between the ages of 1 and 5 years. It especially affects the adenopathies of the head and neck, although it can affect any other area. As discussed in Chapter 17 (extrapulmonary TB), the most important differential diagnosis is with lymphadenitis caused by *M. tuberculosis*. The *M. avium* complex is isolated in 70% to 80% of lymphadenitis cases caused by environmental mycobacteria. In Australia and the United States, the second most common species is *M. scrofulaceum*, while in Northern Europe, it is *M. malmoense*. In children under 5 years, *M. tuberculosis* is isolated in only 10% of cases of peripheral lymphadenitis caused by mycobacteria, with *M. avium* and *M. scrofulaceum* isolated in the remaining 90%. Conversely, *M. tuberculosis* is isolated in 90% of adults with this clinical manifestation. Knowledge of these epidemiological differences between adults and children is very important, since the majority of environmental mycobacteria that cause lymphadenitis in children are very resistant to antituberculous drugs. In addition, since it is a localised
disease, surgical excision is required. In contrast, when \textit{M. tuberculosis} is isolated, this type of surgery is not recommended in both adults and children, and medical treatment is preferred. These data emphasise the importance of culturing the samples obtained by biopsy or thin needle aspiration (the only way to obtain a definite diagnosis), rather than just sending the specimens to the anatomic-pathological laboratory.

**Infections of the skin, soft tissue, and bones**

The species that most frequently cause infections of the skin, soft tissue, and bones are \textit{M. fortuitum}, \textit{M. abscessus}, \textit{M. marinum}, and \textit{M. ulcerans}. These normally occur after trauma injuries, although nosocomial infections in intravenous or intraperitoneal catheters, mammoplasty, or heart bypass surgery have also been described. \textit{M. marinum} causes swimming pool granuloma, which is characterised by a single papule-shaped lesion on an extremity (knee, shoulder, the back of hand, or sole of the foot).

**Disseminated disease**

There are two possible presentations of disseminated disease. The first affects patients who are not suffering from AIDS but who are immunosuppressed (e.g., those with neoplasias, who have received a transplant, or who are undergoing prolonged steroid treatment), and the most frequently isolated organisms are the \textit{M. avium} complex and \textit{M. kansasii}. \textit{M. avium} complex causes fever of unknown origin, while \textit{M. kansasii} generally causes subcutaneous nodules and abscesses that drain spontaneously. Mortality is directly related to the type and severity of the underlying disease. The second presentation affects severely immunosuppressed AIDS patients (CD4 count < 50 cells/mm$^3$), and the most commonly isolated organism is again the \textit{M. avium} complex, which also causes a disseminated infection accompanied by a high temperature, night sweats, weight loss, abdominal pain, and diarrhoea. \textit{M. kansasii} can also be a common cause of disease. The diagnosis can frequently be made with a haemoculture of a blood sample (sensitivity of approximately 90%), making it necessary to culture the samples.

**Culture methods, identification, and sensitivity tests**

**Culture methods**

At least three sputum samples are necessary, and these must be incubated in one or more solid media and one liquid medium. In the case of blood
samples, a simple medium using Bactec 13 A broth or lysis centrifugation with 7H10 or 7H11 can be used. There are two solid media available: an egg-potato base medium (Löwenstein-Jensen agar) and a free agar base medium (Middlebrook 7H10 or 7H11 agar). Quantification of growth (normally from 0 to 4+) is important in order to assess clinical significance and response to treatment. The Middlebrook 7H10 or 7H11 medium is the solid medium of choice due to the easy recovery and quantification of the *M. avium* complex. The Löwenstein-Jensen medium, although excellent for recovering *M. tuberculosis*, is generally inferior to the Middlebrook agar in the case of the *M. avium* complex. In low- and middle-income countries, only solid media are indicated, preferably the Löwenstein-Jensen agar.

The greatest difference in culture techniques for environmental mycobacteria is the need to incubate skin or soft tissue samples at two different temperatures: 35ºC and 28-32ºC. This is because a considerable amount of common pathogens found in these tissues, including *M. haemophilum*, *M. ulcerans*, *M. marinum*, and *M. chelonae*, only grow at low temperatures.

**Identification**

Traditional identification of environmental mycobacteria was based on a series of characteristics and a range of biochemical reactions. The niacin test was the most useful for differentiating between these mycobacteria (niacin-negative) and *M. tuberculosis* (niacin-positive). Runyon described the first classification of nontuberculous mycobacteria based on their growth characteristics and pigments produced. Traditional biochemical reactions are extremely slow, so most laboratories in industrialised countries use other methods to identify the different species, such as high-performance liquid chromatography (HPLC) (fingerprint patterns), the Bactec-NAP test (selective inhibitor of *M. tuberculosis* growth), and DNA tests.

The above-mentioned identification methods are not recommended for use in low- and middle-income countries because they are very expensive and because the diseases caused by these mycobacteria occur very infrequently. In these countries, the classification of mycobacteria according to their speed of growth in Löwenstein-Jensen medium (slow- and fast-growing) and their capacity to produce pigments (scotochromogen, photochromogen, and non-chromogen) can still be used. Based on this simple and rudimentary classification, it is possible to obtain an accurate description of the species and, more importantly, a guide to the type of treatment needed.
Susceptibility tests

As far as antimicrobial sensitivity tests are concerned, there are some recommendations on when, how, and which species these should be carried out. In the case of the *M. avium* complex, this is a matter of some controversy, as *M. avium* complex strains are almost always resistant to low doses of isoniazid, rifampicin, streptomycin, and ethambutol, which are normally used in *M. tuberculosis* sensitivity tests. For this reason, the sensitivity tests for normal antituberculous agents are not recommended for the *M. avium* complex. Neither should they be carried out during initial treatments with clarithromycin or rifabutin. Their use is only indicated in samples from patients who have received previous treatment or prophylaxis containing a macrolide.

*M. kansasii* is initially sensitive to rifampicin, but acquired resistance has been described. Consequently, *in vitro* sensitivity tests should be carried out when a patient relapses or when treatment fails. A more controversial issue surrounds the question of whether these sensitivity tests should be carried out at the beginning of treatment, due to the different behaviour of the drugs *in vitro* (frequent resistance) and *in vivo* (effective if combined with others). For this reason, at least in the case of immunocompetent patients, these sensitivity tests may serve to confound rather than help. They may be useful at the beginning of treatment for AIDS patients, provided the results are interpreted correctly. In addition, the sensitivity of cultures resistant to rifampicin must be determined with the new macrolides, quinolines, and aminoglycosides.

For other slow-growing mycobacteria, the sensitivity tests should include macrolides (clarithromycin, azithromycin), quinolines (ciprofloxacin, ofloxacin, levofloxacin), rifampicin, ethambutol, and isoniazid—some of these drugs could be useful in specific cases if the results are correctly interpreted.

Sensitivity tests are also very useful in diseases caused by fast-growing mycobacteria, and can form the basis for treatment. These sensitivity tests should be carried out with antibiotics such as clarithromycin, azithromycin, cefoxitin, and doxycycline, and not antitubercular drugs.

### Treatment of diseases caused by environmental mycobacteria

The choice of treatment will depend on three fundamental factors: 1) the type of clinical presentation; 2) the species of mycobacteria responsible; and
3) the patient’s immune state (Table 27). In vitro resistance to the majority of front-line antituberculous drugs is one of the most surprising characteristics of these mycobacteria, which, until recently, justified the need for aggressive treatments using up to five or six drugs for long periods of time, as well as the need for surgical excision in cases of localised lung disease. Despite current progress in this area, current treatment of diseases caused by environmental mycobacteria is quite complex, and should only be carried out in specialised centres by expert staff.

Table 27. Treatment of diseases caused by the principal environmental mycobacteria

<table>
<thead>
<tr>
<th>Type of environmental mycobacteria</th>
<th>Clinical form</th>
<th>First-choice treatment</th>
<th>Alternative treatment</th>
<th>AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. avium</em> complex</td>
<td>Disseminated</td>
<td>Clarithromycin; azithromycin + rifabutin; rifampicin + ethambutol</td>
<td>Quinolines Clofazimine Amikacin Streptomycin Isoniazid Streptomycin Ethionamide Quinolines Clofazimine Amikacin</td>
<td>Rifabutin or clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Pulmonary</td>
<td>Clarithromycin; azithromycin + rifabutin; rifampicin + ethambutol</td>
<td></td>
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<tr>
<td><em>M. kansasii</em></td>
<td>Pulmonary</td>
<td>Isoniazid + rifabutin; rifampicin + ethambutol</td>
<td>Clarithromycin Streptomycin Sulphamethoxazole Clarithromycin Streptomycin Sulphamethoxazole</td>
<td>Rifabutin or clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Disseminated</td>
<td>Isoniazid + rifabutin; rifampicin + ethambutol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphadenitis</td>
<td>Surgical</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. fortuitum</em></td>
<td>Cutaneous infections</td>
<td>Surgical</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. chelonae</em></td>
<td>Surgical wounds</td>
<td>Amikacin + cefoxitin</td>
<td></td>
<td></td>
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<tr>
<td><em>M. abscessus</em></td>
<td>Cutaneous</td>
<td>Clarithromycin + aminocycline; doxycycline + trimethoprim-sulphamethoxazole; rifampicin + ethambutol; surgical</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. marinum</em></td>
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Treatment of disease caused by the *M. avium* complex

Not all mycobacteria have the same range of sensitivity; the *M. avium* complex stands out as having the highest degree of resistance. The first studies
on the treatment of the *M. avium* complex in HIV-infected patients showed that treatments involving four drugs (ethambutol, rifampicin, ciprofloxacin, and clofazimine) were effective in reducing bacteraemia and improving symptoms. However, the most important progress in therapeutics was made in the early 1990s when new macrolides were introduced. These drugs were quickly used for the treatment of this infection, owing to their excellent *in vitro* action and because they reached high intracellular concentrations, which is important given that most mycobacteria reside inside the phagolysosome of the macrophages. Rifabutin, a semi-synthetic derivate of rifampicin, has also become a basic component in the treatment of the disease caused by the *M. avium* complex and has proved to be more active *in vitro* than rifampicin.

These data suggest that macrolides are currently a fundamental part of the treatment used for disease caused by the *M. avium* complex as well as by the majority of other slow-growing environmental mycobacteria. Treatment is based on the combination of a minimum of three drugs: 1) clarithromycin (500 mg, twice daily) or azithromycin (250 mg/day or 500 mg three times/week); 2) rifabutin (300 mg/day) or rifampicin (600 mg/day); and 3) ethambutol (25 mg/kg day for 2 months, followed by 15 mg/kg per day). Patients older than 70 years and those with a low body mass tolerate clarithromycin well at doses of 250 mg/12 hours, or azithromycin at doses of 250 mg/three times per week. Other drugs that could potentially be used are quinolines, clofazimine, amikacin, and streptomycin. These drugs, however, are frequently associated with adverse effects that require changes in the treatment. Furthermore, there are drug interactions between rifampicin and protease inhibitors in HIV-infected patients. Rifampicin and, to a lesser extent, rifabutin increases the hepatic metabolism of these drugs, thus resulting in subtherapeutic levels, treatment failure, and acquired resistance to these protease inhibitors.

Patients with a CD4 count of less than 50 cells/mm$^3$ are considered to have an increased risk of disseminated infection caused by the *M. avium* complex. These patients may therefore benefit from primary prophylaxis, which can be carried out using three drugs: 1) rifabutin, which induces the metabolism of antiproteases and requires that infection by *M. tuberculosis* (masked monotherapy) be ruled out; 2) clarithromycin, which is well tolerated and more effective; and 3) azithromycin, which is more effective than rifabutin. Macrolides are associated with one inconvenience—the appearance of resistant strains in 11% to 58% of all cases in which prophylaxis fails, a phenomenon that has not been observed with rifabutin. The primary role of
macrolides in the treatment of disseminated infection, as well as cross-resistance between the different drugs in this group, greatly limit prophylaxis. No specific guidelines have been defined, and treatment should be determined on a case-by-case basis.

In immunocompetent patients it is possible to observe various clinical forms of presentation (e.g., pulmonary, lymphatic), and when the lungs are affected there may be different patterns with different clinical evolutions. The most common type has been the fibrocavitary form of the disease, which affects both upper lobes and can be found predominantly in older men (frequently alcoholics) with underlying lung disease. These cases evolve progressively over 1 to 2 years. Another type of presentation is the bilateral or interstitial nodular form, which is found mainly in older women with no previous lung pathology. This form predominantly affects the medium lobe and lingula, and has a characteristically slow clinical and radiological evolution of 5 to 10 years. It is not known at what stage these patients should be treated. The heterogeneity of the clinical forms of lung disease caused by the *M. avium* complex; the stability of the disease; patient age; and the sequelae, tolerance, and long duration of the antibiotic treatment all make it necessary to carry out a thorough evaluation before deciding on when to begin treatment. Treatment is based on the same three-drug combination described before: 1) clarithromycin or azithromycin; 2) rifabutin or rifampicin; and 3) ethambutol. Patients with an extensive form of the disease are treated at intervals with streptomycin during the first 2 to 3 months, and the dose will depend on the age and weight of the patient. No maximum treatment time has been established, but it is generally accepted to be 12 months after the cultures have proved negative. There should be some clinical improvement after 3 to 6 months of treatment. If this is not the case, resistance or intolerance should be suspected. If the treatment is not successful (due to intolerance or resistance), treatment using a combination of four drugs can be tried: isoniazid (300 mg/day), rifampicin (600 mg/day), ethambutol (25 mg/kg/day for the first 2 months and then 15 mg/kg/day), and streptomycin during the first 3 to 6 months of treatment.

Surgery may be attempted in cases of localised pulmonary involvement by the *M. avium* complex in patients who respond poorly to treatment or who have become treatment resistant. However, the bilateral nature of the disease, the existence of pre-disposing diseases, advanced age, and high morbidity and mortality do not render this treatment very recommendable. Surgical removal in children with cervicofacial or mediastinal lymphadenitis caused by these mycobacteria can be recommended, with or without the need for
additional treatment. Patients with a high surgical risk can undergo treatment similar to that used for the localised pulmonary form of the disease.

**Treatment of disease caused by *M. kansasii***

*M. kansasii* is the second most common cause of lung disease caused by environmental mycobacteria, as well as its most common clinical manifestation. Although it is a less virulent pathogen than *M. tuberculosis*, its clinical and radiological manifestation is very similar to TB (Figure 34). An increase in the number of *M. kansasii* strains resistant to rifampicin has been reported, due in part to the HIV epidemic as well as to inadequate treatment guidelines that use only one or two effective drugs.

Before the introduction of rifampicin, disease caused by *M. kansasii* was treated with isoniazid and ethambutol for 18 months, with the frequent recommendation of surgical treatment to better prevent relapses. Surgery was never proven to provide any benefits. At present, the American Thoracic Society and the British Thoracic Society are in disagreement over treatment guidelines. While the American Thoracic Society recommends the combination of isoniazid (300 mg), rifampicin (600 mg), and ethambutol (25 mg/day in the first 2 months, followed by 15 mg/day) daily for 18 months, including at least 12 months of negative cultures; the British Thoracic Society recommends a treatment of 9 months with rifampicin and ethambutol for immunocompetent patients, prolonging treatment to 15 to 24 months in patients with low host defences. The British Thoracic Society does not recommend the use of isoniazid because of (1) limitations in sensitivity tests and (2) no significant differences in the number of relapses among patients undergoing the British recommended treatment and those undergoing treatment that includes isoniazid. Despite these official recommendations, various studies have demonstrated the effectiveness of short-term treatments.

Clarithromycin shows excellent *in vitro* activity against *M. kansasii* and should be considered in cases of intolerance to any of the previously mentioned drugs. Pyrazinamide should never be used because of proven resistance to this drug.

The majority of patients with an *M. kansasii* infection that is resistant to rifampicin and isoniazid, including HIV patients, respond to a four-drug treatment comprising high doses of isoniazid (900 mg), ethambutol (25 mg/kg), sulphonmethoxazole (1 g, three times daily), and an aminoglycoside other than streptomycin or amikacin, until 12 months of negative cultures have been obtained. It should also be evaluated whether or not clarithromycin should be included.
The treatment of extrapulmonary disease in adults is the same, although in the case of lymphadenitis in children surgical excision is the treatment of choice. Managing this disease in patients co-infected with HIV is complicated by the fact that they are also being treated with protease inhibitors, which suggests that it is advisable to replace rifampicin with rifabutin or clarithromycin.

**Treatment of disease caused by other diseases produced by other slow-growing environmental mycobacteria**

The therapeutic focus of diseases caused by the remaining slow-growing environmental mycobacteria varies greatly, depending on the species that produces the clinical manifestation and antimicrobial sensitivity. There are many uncertainties about when and how treatment should be started, and how long it should be continued. What is certain is that expert personnel must carry out treatment in specialised centres. Most treatment for disease caused by these other environmental mycobacteria is based on that recommended for the *M. avium* complex, with certain modifications for each organism.

Treatment of disease caused by *M. marinum* may range from a simple search for small lesions, to the use of antituberculous and other antibiotic agents, or even surgical excision. Suitable treatment would include clarithromycin, aminocycline, or doxycycline; trimethoprim-sulphamethoxazole or rifampicin; and ethambutol for 3 months.

*M. malmoense* is characterised by a slow growth and non-pigmented colonies, with the majority of cultures sensitive to ethambutol, rifampicin, and streptomycin. A treatment regimen of four drugs is recommended.

*M. simiae* is the only niacin-positive environmental mycobacteria. The majority of the cultures of this type are resistant to the front-line antituberculous drugs; hence, treatment with clarithromycin, ethambutol, rifabutin, and streptomycin is recommended, and can be modified in relation to the results of sensitivity tests.

*M. szulgai* is generally sensitive to rifampicin and to high concentrations of isoniazid, streptomycin, and ethambutol, which is the recommended treatment.

The recommended treatment for *M. xenopi* should include ethionamide, streptomycin, and ethambutol or rifampicin.
Treatment of disease caused by fast-growing environmental mycobacteria

Most cases associated with infection by fast-growing environmental mycobacteria are sporadic and community acquired, although nosocomial epidemics and infections associated with mammoplasty and cardiac surgery wounds have been described. The majority of these infections (> 90%) are caused by three species: *M. fortuitum*, *M. abscessus*, and *M. chelonae*. These species are resistant to all antituberculous drugs, although they are sensitive to a series of standard antibiotics. There are no clinical tests for comparing the different therapeutic treatments, but due to the variability in sensitivity among the different species and subgroups, it is necessary to carry out *in vitro* sensitivity tests (including the most of the standard antibiotics) so that appropriate treatment can be chosen. This will vary according to the form of presentation.

Cutaneous infection is usually due to trauma or surgical infection, and many cases may cure spontaneously or after surgical debridement. In cases of severe infections caused by *M. fortuitum* or *M. abscessus*, intravenous treatment with amikacin is recommended (10-15 mg/kg, given in two doses) and cefoxitin for a minimum of 2 weeks. Imipenem is a reasonable alternative to cefoxitin if the cultures of *M. smegmatis* and *M. chelonae* are resistant to this drug. For *M. chelonae*, tobramycin is more effective *in vitro* than amikacin, which in turn should be used in combination with cefoxitin or imipenem. In patients with serious infections, 4 months of treatment is recommended, whereas in the case of bone infections, treatment duration increases to 6 months. Surgery is recommended when there is widespread infection, formation of abscesses, or treatment is difficult.

In the case of pulmonary infections caused by fast-growing mycobacteria, *M. abscessus* is the responsible agent in 85% of isolations, although in patients with gastroesophageal involvement *M. abscessus* and *M. fortuitum* are isolated with the same frequency. Sensitivity tests are also essential when treating infections caused by *M. abscessus* and *M. fortuitum*, with 6 to 12 months of treatment being adequate. The natural history of the disease depends on the underlying disease. In the case of *M. abscessus*, most patients without an underlying disease have a painless, slowly progressive course, whereas in patients with gastroesophageal complaints, disease may progress rapidly and be devastating, causing death in 20% of cases.
Management of diseases caused by environmental mycobacteria in low- and middle-income countries

How this group of diseases is managed in developed countries is completely different with respect to low- and middle-income countries. In richer countries, although these diseases are more common (competing with *M. tuberculosis*), all the diagnostic (liquid culture media and a range of sensitivity tests) and therapeutic resources are available. Furthermore, procedures very similar to those described in this chapter can be used. In countries with fewer resources, however, these diseases are much less common, so dedication of limited resources to sophisticated diagnostic methodology cannot be justified and optimisation of current treatments is therefore necessary.

In low- and middle-income countries, cultures should only be done in solid Löwenstein-Jensen medium. Some simple biochemical tests, if available, can also be performed. Sensitivity tests will not be necessary if resources are not available. The important decision is whether the patient should be treated or not, and with which combination of drugs. The decision to treat (colonisation vs. disease) will depend on the physician caring for the patient. However, it is impossible to adapt the methods described in this chapter for use in poorer countries. Still, it could be argued that for adequate handling of this group of diseases, it is possible to make a rudimentary classification that will serve as a relatively accurate guide for treatment by using culture with the Löwenstein-Jensen medium and its exposure to light and darkness. In this way, the mycobacteria can be classified in four main groups:

1. The *M. tuberculosis* complex. Easily identifiable using simple biochemical tests (niacin). Patients will receive a standard treatment such as those outlined in Chapter 9.

2. Fast-growing mycobacteria. All of these grow in the Löwenstein-Jensen medium in less than 7 days, which distinguishes them from the other mycobacteria. All patients can be treated in the same way, with a minimum margin of error, using amikacin (10-15 mg/kg, given in two doses) and intravenous cefoxitin, for a minimum of 2 weeks. In patients with serious infection, a minimum of 4 months of treatment is recommended; in the case of bone infection, the length of treatment increases to 6 months. When treatment is prolonged, the addition of vibramycin, clarithromycin (or azithromycin), and a second-generation oral cephalosporin should be considered.

3. Slow-growing mycobacteria (more than 1 week) that change colour when exposed to light (photochromogens). Most cases will be caused by
M. kansasii; thus, a treatment including isoniazid + rifampicin + ethambutol for 12 months will cure most patients.

4. Slow-growing mycobacteria (more than 1 week) that do not change colour when exposed to light (non-photochromogens). This group will include all non-chromogens (do not change colour) and the scotochromogens (change colour in the dark). The most important species in this group is the M. avium complex, although the rest respond very well to the same treatment. A treatment of ethambutol + rifampicin (rifabutin is very complicated to use and costly to obtain) + clarithromycin for 18 months for this entire group offers a high probability of success.

Recommended reading

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