Part III

TUBERCULOSIS

A BACKGROUND PAPER FOR THE ADULT LUNG HEALTH INITIATIVE

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1. EPIDEMIOLOGY

1.1 Case definition

A case of tuberculosis is defined as a patient who presents with a clinically detectable disease, caused by tissular lesions due to *Mycobacterium tuberculosis*. This general definition in fact covers several important definitions for the epidemiology of tuberculosis:

(a) cases of pulmonary tuberculosis whose sputum contains sufficient bacilli to be detected by direct microscopic examination of the sputum (or of the product of gastric lavage). These are the most infectious cases, classified as cases of smear positive pulmonary tuberculosis.

(b) cases of pulmonary tuberculosis whose sputum contains few bacilli detected by growth in culture after 4 or 6 weeks rather than microscopic examination of the sputum. These are much less infectious cases, classified as cases of smear negative culture positive pulmonary tuberculosis.

(c) the few cases of smear negative culture negative pulmonary tuberculosis (observed in children and young adults) can only be identified by the clinical and radiologic abnormalities observed.

(d) finally, the cases of extra-pulmonary tuberculosis are generally identified by clinical and/or radiologic signs, biological modifications of the LCR or of pleural, pericardial or peritoneal exsudates, and generally can only be confirmed by specimen culture, or from histology of biopsy material. These cases are not infectious.

The natural history of tuberculosis shows that the cases of smear positive pulmonary tuberculosis are the principal sources of transmission *Mycobacterium tuberculosis* within the community.

1.2 Burden of disease

According to WHO estimates, approximately 1/3 of the world's population is infected by *Mycobacterium tuberculosis*. This infection is detected by a positive coetaneous reaction to the tuberculin. The works of Canetti (1939, 1972) show that most people who have been infected and who have a positive skin test to the tuberculin harbour viable bacilli in their bodies. But not all infected subjects become ill: the infection is most often latent, and not accompanied by symptoms indicative of active disease. The number of primary infections and reinfections occurring depends on the density sources of infection present in the community. Among the 1,800 million human beings currently infected 20 to 30 million people will develop the disease tuberculosis within the next ten years.

In 1995, WHO estimated that 7.4 million cases of active tuberculosis occurred, almost half of which were infectious cases of smear positive pulmonary tuberculosis (incidence). According to the case notification rates to WHO, 3.3 million cases of all forms of active tuberculosis were detected, including 1.15 million smear positive pulmonary tuberculosis cases. Therefore, tuberculosis cases, and notably infectious cases are most likely underdetected.

Given the duration of the natural course of the untreated disease, one can estimate that the prevalence of the disease was between 15 to 20 million, that is, the total number of cases in the world living with active tuberculosis in 1995. These figures suggest that the burden of tuberculosis will be felt by mankind for many years to come. Those already infected are the programmed patients of tomorrow. They will continue to exist, carrying viable bacilli as long as not all active cases (or for that matter infectious cases) are detected.

The mortality due to tuberculosis is estimated at 2.9 million deaths per year. Deaths due to tuberculosis account for 25% of preventable deaths in developing countries.

1.3 Distribution in the world

1.3.1 95% of the cases of active tuberculosis and 98% of deaths by tuberculosis occur in the "developing" countries of Asia, Africa and Latin America. Given the age structure of the populations of these countries with a high incidence of tuberculosis, the disease primarily affects adults between 15 and 50 years of age (75% of cases) and especially young adults between 20 and 40 years of age, i.e., an age group whose social and economic activity is the most significant, and where the number of young children in families is the highest.

1.3.2 The world-wide distribution of tuberculosis varies greatly depending on the country:

(a) In high-income countries with a high level of human development, tuberculosis declines consistently, despite a recent inflection of the curves due socio-economic factors in specific sub-groups of the population in rich countries, or to the dismantling of health services in the countries of Eastern Europe. The annual rates for notified cases of all forms of tuberculosis are between 10 to 50 per 100,000 population. In these countries, the majority of infected subjects are older than 50 year of age. The means available make it possible to cure all patients, even those belonging to high-incidence groups (migrants, refugees, the poor) when adequate measures are applied.

(b) In low or middle income countries, the annual rates for cases of tuberculosis reported are between 50 and 400 per 100,000 population. Tuberculosis (in absolute number of patients) spreads even when the rate of cases per 100,000 population stagnates or sometimes regresses. The continuous spread of tuberculosis is the result of the persistence of several uncontrolled sources of infection in the population. In addition to this, several factors facilitate and contribute to the transmission of *Mycobacterium tuberculosis*:

(i) *poverty*, which affects more than one-third of the population: this rate has not changed over the last 10 years.

(ii) *rapid population growth* and the age structure of the population, particularly in Africa, in the Middle East and in Southeast Asia.

(iii) *migrations*: in-country migration, from rural areas to urban areas (for economic reasons), internal displacements (for reasons of famine and safety), or international migration (refugees, migrant workers) with their consequences (substandard housing, overcrowding, malnutrition, which encourage transmission of the disease).

(iv) *inadequate health services*. First, inadequate in terms of inaccessibility: Despite the efforts and declarations of Alma Ata in 1978, the health services are not always capable of meeting the needs of the most vulnerable groups of society. The means available do not allow detection or cure of more than 50% of existing cases. Secondly, inadequate in terms of improperly managed. TB burden is amplified in countries that do not support a TB control policy. Wrong prescription practices and uncontrolled TB drug distribution enable the emergence of drug resistant bacilli in TB patients and the transmission of drug resistant bacilli into the community. When a patient has multi-drug resistant TB, (i.e. resistance to at least INH and Rifampicin), the chances of cure are reduced, especially in the poorest countries where the available resources for health services are usually insufficient for a proper management of this category of TB patients.

(v) and finally, in certain countries, *the HIV-AIDS epidemic*, which has raged since the beginning of the 1980's, and which currently increases the number of tuberculosis cases anticipated in these countries from 10 to 50%.

1.3.3 But poverty, demographic changes, health system failure and the HIV-AIDS epidemic are not the only causes of the "resurgence" of tuberculosis since 1993, the year when the WHO declared tuberculosis to be a global emergency. It must also be noted that in the African countries where programs established to fight tuberculosis were weak or nonexistent, the re-establishment of programs during the last ten years has allowed detection of increasingly numerous cases (particularly in cities) owing to easier access to health services and thanks to the implementation of a TB control strategy focused on the detection and effective treatment of infectious cases.

1.3.4 The available epidemiological data underline the need for more precise analyses with an operational impact on tuberculosis control, and specifically of:

(a) gender differences in tuberculosis morbidity, not only in low income countries. These differences are multicausal, depending on risk of exposure, risk of infection given exposure, risk of disease given infection, and finally access to diagnosis and

treatment given disease. The role of pre-existing infection prevalence is a basic determinant. But other factors (socio-economical, cultural, accessibility to an efficient PHC system) should also be considered.

(b) the distribution of tuberculosis cases in cities and urban centers. In many developing countries, the urban population of large cities, which represents 10% to 30% of the total population of the countries, supplies 30% to 50% of the cases of tuberculosis detected in the countries under consideration.

This excess morbidity linked to an unstable urban environment leads to an overload for the already inadequate health services, and raises new problems for the organization of health services (which the development of a private sector cannot resolve) and for preventing the emergence of drug-resistant tuberculosis (associated with poor medical practices).

1.4 Etiology

Tuberculosis is an inter-human infectious disease that is transmitted by aerial route. It passes from a patient who excretes bacilli to non-ill subjects (not previously infected, or already infected). It is the very epitome of a social disease whose frequency is linked to transmission encouraged by overcrowding. The reservoir of infection is located exclusively in the lungs of the diseased patient. Efficient transmission is linked to the number of infectious sources present in a community, but more so to the number of people living in the same room with a source of infection. Poverty, which leads to overcrowded housing and poor nutrition, is therefore the basic condition for the occurrence and the persistence of tuberculosis. Other conditions are concomitant or encouraging factors: the collapse of the immune defense mechanisms of individuals (particularly following HIV infection), psychological stress linked to changes in social situation (migrants, refugees, loss of employment)...

The fight against tuberculosis, for which an effective strategy is now available, is one of the elements of programs against poverty.

1.5 Pathogeny

1.5.1. The transmission of tuberculosis in humans most generally has two stages. A source of infection, that is, a patient afflicted with pulmonary tuberculosis transmits via aerial route (by coughing or sneezing) infectious particles from the bronchial secretions sprayed by forced expiration. The disease is transmitted to the individuals most exposed: those close by, usually the members of the family, those who live and sleep in the same room as the patient. When one or more bacilli enter into the lungs of a subject who has not been infected up to this point, there is a non-specific inflammatory reaction around the bacilli. This is the "primary complex": a parenchymal pulmonary lesion and a swollen mediastinal lymph node nearby, beside the bronchi. These lesions generally heal spontaneously once, within 2 to 6 weeks, a specific allergic reaction and cellular immunity develop. However, before these reactions occur, bacilli carried by the macrophages into the lymphatic system and subsequently into the blood circulation,

can create secondary foci in all the organs (kidneys, bones, joints, spine, serosa, and brain) and cause severe forms of tuberculosis (miliary, meningitis) that are seen more often in children before the age of 5 than in adolescents and adults.

The disease tuberculosis can develop several weeks or several years after the primary infection: either progressively at the site of the initial primary infection, or, more often, over the 10 years that follow, after reactivation of postprimary foci where latent bacilli survive, and even after exogenic re-infection (resulting from massive or repeated contact with a source of infection).

This explains why the process of eliminating tuberculosis in a community is very slow: There is always a risk that latent infections (through re-activation of primary infection or re-infections) are at the source of a case of active tuberculosis, even when the BCG vaccination is used on a massive scale.

1.5.2 Knowledge of these basic data has consequences for the diagnostic and treatment strategies in tuberculosis control. Of the available diagnostic strategies, the tuberculin skin test has only limited utility, since it does not allow one to distinguish between infection and disease, neither does its negativity rule out active disease. On the contrary, identification by microscopic examination of acid-fast bacilli present in the sputum smear of a patient is the quickest and most important method in practice for detecting the most infectious cases of tuberculosis.

The culture of sputum samples (or other specimens taken by puncture or by biopsy) allows confirmation of cases of pulmonary tuberculosis or extra-pulmonary tuberculosis that were negative on microscopic examination.

But sometimes, in extra-respiratory visceral forms of tuberculosis and in children, it is not always possible to access the lesions directly or to obtain significant pathological products: it is in these cases that the clinical symptoms, the biological changes (including the tuberculin skin test) and the radiologic changes (observed on standard x-rays of the thorax and of the bones; following injection of contrast for visualisation of the digestive tract, kidneys or the female reproductive system; or seen by tomodensitometry for brain or liver) provide presumptive arguments for the diagnosis that require medical interpretation.

For treatment strategies, the various forms of tuberculosis are not equally severe. The patients to be considered priorities for treatment are:

- those who are the most infectious, i.e., those who excrete a sufficiently large number of bacilli to be identified by smear microscopy.

- and those who are afflicted with severe forms of the disease that are an acute threat to the life of the patient (meningitis, acute miliary) or that ultimately result in a severe functional handicap.

2. CARE PROVISION

2.1 Objectives

The general aim of the fight against tuberculosis is to reduce the mortality, the morbidity and the transmission of the disease until it no longer constitutes a public health threat.

To accomplish this, absolute priority should be given to the detection and cure of cases of sputum smear-positive pulmonary tuberculosis. The WHO strategy, adopted by the World Health Assembly in 1993, sets two targets:

- to detect at least 70% of existing infectious cases
- and to cure at least 85% of the cases of smear positive tuberculosis detected.

These two goals are closely linked, if one wants to achieve the overall objective:

- After all, to give priority to the detection of infectious cases, without ensuring that one can achieve a high rate of cure, risks creating more chronic cases and cases of drug-resistant tuberculosis that are difficult to cure.

- Conversely, to achieve a high cure rate for only 10 to 20% of infectious cases, and to continue to detect and to treat as a priority a majority of non-infectious cases does not reduce the size of the pool of infection sources, and diverts available human and financial resources toward non-priority goals.

2.2 Health system structure

With regard to the detection and treatment of tuberculosis, the tasks of the various levels of public (or private) health services are different:

2.2.1 The tasks of the most peripheral services (health posts manned by nurses or nurses' aids; health centers with general practitioners; as well as private practitioner's practices) are to identify tuberculosis suspects and, when the diagnosis is documented, to manage the patient's treatment until cured. In addition to this, another task is to provide tuberculosis screening for those close to the patient.

2.2.2 At the district level, the diagnosis of tuberculosis must be documented with certainty by a qualified, trained and monitored staff:

- at least in a clinical laboratory that provides tuberculosis microscopy (one per 100,000 to 200,000 population on average), accessible to suspected cases as well as to patients during treatment or to health personnel from peripheral services transporting pathological samples collected from patients.

- and, if possible, in the general hospital or health center of the district with radiology equipment where the medical staff must be capable of confirming the diagnosis of smear negative pulmonary tuberculosis, extra-pulmonary tuberculosis and childhood tuberculosis.

At this level, the district register of TB cases is regularly completed and audited by the district coordinator. The prescription of appropriate therapeutic regimens is decided in accordance with the guidelines of the national program. The place of treatment is selected in conjunction with the patient and according to the identified skills of the medical staff working in the medical facilities closest to the patient's home.

2.2.3 Finally, at a higher level than the district (i.e. region or county level), the reference center (i.e. hospital or specialized health clinic) is situated, where complex cases of tuberculosis are referred to. Such cases include for instance complications of the disease itself, major adverse reactions due to the toxicity of the medication, failures and relapses after application of a standardized treatment. These are entrusted to a reference consultant (a specialist or non-specialist doctor), who cooperates closely with the district coordinators.

2.3 Diversity of the actual situations

In view of different socio-economic and health system's realities observed in the various countries, the accomplishment of the provision of care (diagnosis and treatment) to tuberculosis patients is subject to highly variable terms and conditions.

Differences observed are linked to:

- Access to information (about symptoms that lead one to suspect tuberculosis and about the possibility of having recourse to a competent health service), by the population in general and families in particular. When health services are non-existent or too far away, specially trained community health officers and community groups can assist in informing patients, encouraging them and guiding them. When these relays do not exist in the community, and when the competence of the health care staff is not recognized by the population, information that is sometimes helpful, but more often partial or biased, is given by unqualified people (informal private sector) who, through different means, inspire trust in the patients and in their families, while delaying entry to competent health services.

- Density of the medical coverage of the population. When the nearest medical facility is more than 5 km from the patient's home, the utilisation of this facility decreases with the distance; the costs of access (in time, in transportation costs) constitute an obstacle to diagnosis and treatment. When the laboratory where the microscopic examinations of sputum samples are performed is more than 20 Km from the patient's home or from the health station where the samples are collected, the patient's chances of receiving a definite diagnosis and well-supervised treatment decrease.

- Competence of health care personnel capable of recognizing the various forms of tuberculosis. The practical skills of health care personnel in selecting tuberculosis suspects, identifying tuberculosis cases, and prescribing and monitoring the tuberculosis treatment are very inconsistent, even when they have earned equivalent degrees. This is why the diagnostic criteria and the therapeutic regimens to be applied must be codified in the national technical guidelines and their application regularly monitored during supervisory visits made by the district and regional coordinators. These supervisory visits are the guarantee of the quality of the health care program for tuberculosis at the district level, regardless of the professional training of the district coordinator (specialist, general practitioner, nurse) and regardless of the conditions under which the health care staff involved practice (public service, non-profit private sector, for-profit private sector).

- Institutional relations between the community structures (municipalities, parishes, elders' councils) and the health services available for the community. In organized human groups, an institutional relationship between the community and the health care services can considerably improve patient counseling, the management and control of health care services, as well as the pertinence of the responses of the health care services to patients' needs. The effective participation of the community in establishing and monitoring health care programs, including the "tuberculosis" program, as part of the application of the "minimum health care package" is a decisive element in the long-term success of the technical activities implemented.

3. DIAGNOSIS

3.1 State of the art technology/options

3.1.1 Equipment, tools needed

(a) **For the bacteriological diagnosis of tuberculosis**, the conventional diagnostic methods are microscopy and culture.

(i) diagnosis by microscopy is carried out either after staining with the Ziehl Neelsen method (hot or cold) or after staining with auramine O (most frequently used method among those based on fluorescence).

- *Ziehl Neelsen staining* requires the use of a binocular microscope that can be used with natural light or electrical power, equipped with an immersion lens (x 100), an eyepiece (x 8 or x 10) and replacement lights.

- *auramine staining* requires the use of a binocular microscope, a unit of lamps emitting blue or UV light, and a dry lens (x 25). Before considering a slide negative, one must also examine [approximately] 300 fields of an immersion lens, which takes 15 minutes with the Ziehl Neelsen method and 2 minutes with the auramine O fluorescent method.

(ii) diagnosis by culture requires additional equipment: biological safety cabinet, centrifuge or agitator, equipment for seeding the culture media, an incubator, and culture media.

- the solid egg medium or *Loewenstein Jansen medium* is the most used due to its high sensitivity and its low cost. Solid Ogawa media and agar media (Middlebrook and 7H11) are also used. The response is obtained in 3 to 6 weeks.

- the *Middlebrook liquid medium* (7H12) also allows detection of mycobacteria.

- A quick detection method for the growth of mycobacteria, radiometric respirometry, is based on the the measurement of the marked CO_2 released by the mycobacteria during their growth in "medium containing as its sole source of carbon, palmitic acid marked with C^{14}". This is the BACTEC method. The response is obtained in 1 to 2 weeks. However, the impossibility of observing the morphology of the colonies, the frequency of contaminations, the cost that is five times higher than that of standard culture methods, and the operational difficulties linked to the disposal of radioactive waste limit the use of the BACTEC system.

The development of *non-radioactive liquid media*, still in the research stage, would allow us to combine the advantages of the speed of the liquid media and the sturdiness of the solid media.

(iii) the other diagnostic methods (sometimes presented as the methods of the future) are not used, nor are they applicable in countries with a high incidence of tuberculosis:

- the *immunological methods* that serve as the basis for the serodiagnosis of tuberculosis have a very poor specificity and a low sensitivity.

- *molecular biology methods* rely on gene amplification. The polymerase chain reaction (PCR) has been improved by the use of specific strains that allow rapid identification of M. tuberculosis, M. avium, and M. intracellular. However, the gene amplification methods used to detect M. tuberculosis in sputum give less impressive results than culture.

  The *analysis of genetic imprints* allows typing of the strains of M. Tuberculosis according to the distribution of the genetic material (chromosome DNA) of these strains. The "Restriction Fragment Length Polymorphism" (RFLP) analysis is used in certain research laboratories to identify the strains isolated in some limited epidemiological surveys. But RFLP is not a current tool of diagnosis.

(b) **The histological diagnosis of tuberculosis**, after mounting and examination of the histological tissue samples taken by biopsy is not specific. Similar formations can be caused by various granulomatoses. However caseating granuloma is highly indicative of tuberculosis: it is only found in cases of active tuberculosis that were not previously treated or that have only been treated for a short time. This diagnostic method requires general histopathology laboratory equipment, and medical or surgical departments capable of taking tissue biopsies under conditions that provide for the safety of the patient.

3.2 Applicability to developing country settings

3.2.1 In the prevailing epidemiological setting in developing countries, the foremost priority is the continual **detection of the maximum number of infectious cases** (i.e., the cases of smear positive pulmonary tuberculosis) in the entire population covered by the health care services.

(a) Since infectious cases can be detected easily by sputum smear microscopy, the establishment of a network of laboratories capable of confirming the diagnosis of tuberculosis is an indispensable prerequisite for any tuberculosis program. These peripheral laboratories must be established on an average of one per 100,000 population in rural areas, and at a rate of one per 200,000 population in urban areas. They can be further decentralized in remote rural areas, if quality control can be assured, at a rate of one per 50,000 population. More extensive decentralization risks leading to a performance decline in the quality of the diagnosis. Normally, these laboratories complete 10 to 50 smear examinations per week, and the Ziehl

Neelsen method is generally used. Several studies have been conducted in the rural and urban environment of countries with a high TB prevalence, showing that the general multipurpose laboratory services can detect by microscopy at least 2/3 of pulmonary TB cases which exist in the community, especially if three sputum smears (one early morning sample and two on-the-spot specimens) are taken from each individual suspected of TB. In urban areas or in large reference hospitals where more than 30 specimens are examined every working day, the fluorescence method can be used. The additional investment costs are offset by greater effectiveness, without any increase in staff or wage costs.

(b) The use of radiologic means has long been presented as an alternative to the limitations of diagnosis by microscopy. It must be underlined that radiographic abnormalities are not specific to tuberculosis, but that they can indicate it more or less strongly depending on the skills and experience of the physician who interprets them. Radiologic means can thus constitute a good means for selecting suspect individuals, especially when the first three smear exams by microscopy are negative, by encouraging that the examination by microscopy be repeated several times. The use of radiologic means (with standard basic radiology equipment or a MMR when there are more than 40 tuberculosis suspects to be examined each day) remains a costly exploratory method, both for initial investments and for recurrent costs (maintenance, films, developer and fixing salt). These means are generally only available in district or regional/county hospitals or in specialized TB and chest clinics, and are used to identify cases of smear negative pulmonary tuberculosis, as well as certain cases of extra-pulmonary tuberculosis (bone, joints, kidney, etc.)

3.2.2 The establishment of **culture laboratories** at intermediate levels (county or regional hospitals, between the national and the district levels) is a secondary stage in the development of the network of tuberculosis laboratories. These laboratories allow confirmation of the diagnosis of tuberculosis in smear negative microscopy cases and in cases of extra-pulmonary tuberculosis where a sample of pathological material (excretion, pus, biopsy) can be obtained. It is at this level – regional and county hospital - that a general histopathology laboratory can be established and can contribute to the diagnosis of some cases of extra-pulmonary tuberculosis.

3.2.3 **"Modern" diagnostic methods** (BACTEC, PCR) have a certain interest in national reference hospitals when the activities of these laboratories include a fundamental research component. But the most important function of reference laboratories is to quantitatively and qualitatively strengthen the network of microscopy laboratories in the country and to validate the results of smear examinations performed at peripheral/district level. This is why the "modern" diagnostic methods neither have a place in the budget nor in the priorities of a national tuberculosis program in a country with a high incidence of tuberculosis.

3.3 Applicability by level of health facility

3.3.1 At the **pre-primary health care level** (families, basic communities), the educated members of the community (schooled, as long as the scholastic programs contain the basic elements of the information concerning tuberculosis) or, for example, members of the management boards of community health services, community health officers and traditional practitioners (after retraining) can assist in

(i) *identifying* individuals suspected of having tuberculosis

(ii) *encouraging and advising* suspects to visit the closest health care facility for confirmation of the diagnosis and subsequent treatment

(iii) *recognizing* the abnormal symptoms in individuals (children or adults) living in contact with a source of infection.

3.3.2 At the **level of health posts and health centers without laboratories**, the health care staff (nurses and sometimes physicians) must be capable of

(i) *identifying*, among the individuals who consult them for general respiratory symptoms, those that are tuberculosis suspects.

(ii) *making sure* that these suspect individuals provide 3 sputum samples to the nearest laboratory or to the health facility that will be responsible for sending the samples to the laboratory.

(iii) *prescribing* appropriate (symptomatic) treatment for patients who have respiratory symptoms.

(iv) *recording* in a treatment register the list of names of tuberculosis cases identified at the higher level.

3.3.3 At the **level of medical facilities with a multipurpose laboratory** where smear examinations can be performed (reference health center, reference health clinic for the district, specialized chest clinic, district hospital) the health care staff (physicians, nurses and laboratory technicians) must be collectively capable of:

(i) *identifying* the cases of tuberculosis to be treated (cases of smear positive and smear negative pulmonary tuberculosis, cases of extra-pulmonary tuberculosis, specific forms of childhood tuberculosis and severe forms of tuberculosis)

(ii) *recording* all the cases recognized in the tuberculosis register (of the district or of the sub-district covered by the laboratory)

(iii) regularly *filling out* quarterly reports regarding the detection of cases and concerning the management of the program and of consumables

3.4 Cost effectiveness of diagnostic options

The goal of implementing diagnostic procedures is to **detect the sources of infection.**

3.4.1 The most effective procedures at the periphery are:

- the *selection of suspected individuals by respiratory symptoms*, whether or not combined with general ones.

- *diagnosis by microscopy* of at least 3 sputum samples from suspected individuals.

3.4.2 For large urban areas, when a specialized center receives a hundred people each day who present with respiratory symptoms, the use of radiologic means (MMR *radiophotography*) can be discussed to improve the selection of suspect individuals and to reduce the work load of the laboratory technicians responsible for microscopy (as well as the possibility of cultures for the suspected cases of smear negative microscopy). Studies of cost effectiveness of different diagnostic strategies can have different results depending on the country, due primarily to the salary levels of more qualified health care personnel (physicians who read radiologic documents, radiology technicians, laboratory technicians trained to make cultures) and the costs of the necessary investments in equipment.

3.5 Indicators for monitoring performance of detection and quality of diagnosis

3.5.1 To measure the performances achieved during the case detection process as well the quality of diagnosis, several indicators need to be collected. For that reason, three information sources need to be consulted in each district:

- the outpatient registers in every health facility (primary health services) where all care seekers are recorded by age, sex and reason for visit;

- the register of laboratory where tuberculosis micoscopy is performed, in which are recorded the suspects from whom one or more smear examinations have been requested for diagnosis;

- the district (or subdistrict) tuberculosis register, in which all identified tuberculosis cases (coming from a definite area) are recorded.

The data that should be collected on a quarterly and annual basis are the following:

- the number of patients seeking care in health facilities;
- of these, the number of adults (aged 15 years and over) presenting with respiratory symptoms;
- of these, the number of adults with respiratory symptoms suggestive of tuberculosis;
- the number of smear microscopy examinations requested and performed for tuberculosis suspects;
- the number of cases of pulmonary (smear positive or smear negative) and extra pulmonary tuberculosis recorded.

3.5.2 From these data, two series of indicators can be calculated:

(a) Indicators for monitoring the case detection process

- the proportion of adults (aged 15 years and over) presenting with respiratory symptoms among the totality of care seekers. This varies from 10% to 30% in developing countries, according to the age and the season; it is always higher among children aged under 5.
- the proportion of tuberculosis suspects among the totality of adults presenting with respiratory symptoms: this proportion differs according to the experience of the health staff and according to whether or not x-ray is used for selection of TB suspects;
- the proportion of tuberculosis suspects, among all of the tuberculosis suspects detected, who have been sent and undergone three sputum smear examinations. This proportion should be over 90% to increase the chances of detecting infectious cases.

(b) Performance indicators in case detection

- the proportion of smear positive cases among all tuberculosis suspects recorded in the laboratory register. If the respiratory symptoms presented by the patient are the only criteria for inclusion as a tuberculosis suspect, the proportion will be on average 10% (range 5-15%). But this proportion can vary depending on the criteria applied to select tuberculosis suspects: duration of symptoms presented by the patients, confirmation (or not) by medical examination, type of medical examination (e.g. x-ray).

- the proportion of new smear-positive pulmonary cases out of all new pulmonary tuberculosis cases (smear positive, smear negative and smear not done) recorded in the district tuberculosis register. This should be at least 65% of cases. If it is less than 65%, the diagnosis of pulmonary tuberculosis (by microscopy, and/or by clinical and radiological symptoms) is of poor quality. The proportion can reach 80% (range 75%-85%) if radiological facilities are available and used appropriately, and if smear microscopic examinations are requested (at least two additional series of three smear examinations for those tuberculosis suspects who have three negative smears in the first serie). A lower proportion can be observed in HIV-positive patients, particularly at later stages of AIDS. However, even in African countries with high HIV prevalence, the overall proportion of smear positive cases among all new pulmonary tuberculosis cases is frequently over 65%.

- the proportion of all smear positive cases (new and relapses) out of all tuberculosis cases recorded in the district tuberculosis register – this proportion should be at least 50% of cases. If it is less than 50%, there is a clear indication that priority in the programme is not given to the detection of infectious cases, and that the performance of the programme is insufficient.

3.5.3 The validity of the data collected depends on compliance with the definition provided by the national tuberculosis programme, on the health staff's skill, and on the quality of supervisory visits at peripheral level and at district level.

When the data processing is regularly and properly performed at district level, it is possible to calculate annually the reported notification rates of new cases of smear positive tuberculosis and of all tuberculosis cases per 100.000 population. The reported rate of new cases of smear positive tuberculosis can be stratified by age and sex: it thus provides data regarding tuberculosis trends over several years.

3.6 Integration into the minimum health care package delivered at the primary health care level

3.6.1 At present, the selection activities for suspected individuals are integrated randomly and empirically according to the skills and experience of the staff in place. Since the tuberculosis program is considered to be a "vertical" "separate" program, staff suffice to refer suspected patients to a specialized center, as they do not feel involved in the consequences of the process. As a result, the patients are not managed, and if they do not have the means to get themselves to the specialized center, the diagnosis is missed. When they are effectively referred, and diagnosed, the diagnosis is not communicated to the service that saw the patient the first time; thus the primary care facility, which is not involved in the diagnosis follow-up, i.e., the treatment, is unaware of the diagnosis of tuberculosis. In fact, the selection activities for suspected individuals should be

integrated into the minimum health care package delivered in primary health care facilities

3.6.2 The aspects that should and could be integrated more effectively are the following:

- selection of suspected individuals by application of a decision tree (or decision algorithm) to all adolescents and adults visiting the health service (whether public or private) with respiratory symptoms.

- management until cure of patients who have respiratory symptoms caused by prevalent respiratory disease, but not suggestive of tuberculosis.

- better coordination (and feedback) between peripheral medical facilities that select tuberculosis suspects and the district facilities where the diagnoses are confirmed (laboratory, control center, hospital), and where the treatment is prescribed.

3.6.3 List of essential drugs, equipment, tools (training and monitoring) needed for intervention

Essential drugs: acetylsalicylic acid, paracetamol, nasal decongestant, codeine or antitussive preparation.
benzyl penicillin, procaine benzyl penicillin, amoxicillin, sulfamethoxazole-trimethoprim, erythromycin, oxytetracycline
salbutamol in nebulizer
dexamethasone in tablet or vial form
beclomethazone in nebulizer

Equipment at peripheral level:
thermometer, timer (for measuring pulse and respiratory rate), balance
sputum containers and transport boxes
peak flow meter

Laboratory equipment:
binocular miscroscope
slides, reagents

Tools for training and monitoring:

At peripheral level:

- Decision algorithms describing the systematic approach for the essential respiratory symptoms:

  - cough without sputum
  - cough with sputum (mucous, purulent, hemoptysic)

- clear hemoptysis
- dyspnea
- fixed side thoracic pain

- Standardized outpatients register (name, age, sex, functional classification (working diagnosis) outcome). This basic register should allow easy monitoring of process and performance. Thus, key words for each of the possible respiratory diseases must be identified. In the case of TB, keyword should be "TB suspect".

At district level:

Technical guidelines for the management of tuberculosis and other respiratory diseases among youth and adults

District tuberculosis register.

At Laboratory level:

- Technical guidelines for microscopy of tuberculosis
- Laboratory tuberculosis register
- Protocol for quality control.

3.7 Role of the private sector

3.7.1 The **non-profit private sector** can be integrally involved in detection activities using the same supports and the same means as the public sector.

3.7.2 The **for-profit private sector** can be involved in applying the program if there is an interest: easy access to a quality controlled microscopy laboratory, possibility of professional relationships with a reference consultant (of recognized quality) and feedback on the patients referred.

4. TREATMENT

4.1 Drugs (State of the Art)

- Current treatment for tuberculosis consists of administering several combined drugs in chemotherapy regimens for six or eight months. The essential anti-TB drugs, when properly administered, allow more than 98% of patients suffering from the disease to be cured. These medicines are isoniazid, rifampicin, pyrazinamide, streptomycin, and ethambutol. In low-income countries, thioacetazone is still used, in combination with isoniazid, but thioacetazone is often substituted with ethambutol as a bacteriostatic drug because of side effects observed in countries where HIV is prevalent.

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Second line reserve anti-TB drugs may be used for patients in whom bacilli persist and have become resistant to the essential anti-TB drugs (especially isoniazid and rifampicin). These second line reserve drugs are ethionamide, quinolones, kanamycin, or other aminosides, cycloserine, and para-aminosalicylic acid (PAS), should be combined in the appropriate regimens, and must be administered for more than 18 months. These second line reserve drugs are much more expensive, often have more side effects, and are always less effective than the essential drugs.

- The goal of chemotherapy regimens is to cure the patient (by reducing the bacilli population he is hosting as drastically and as quickly as possible), to reduce the spread of the disease (by giving absolute priority to the treatment of infectious cases), and to avoid the emergence or selection of bacilli that are resistant to the essential drugs (by combining the main drugs during the first two months of treatment).

- The treatment guidelines currently recommended by WHO may be adapted to the various epidemiological and economical situations encountered throughout the world. The choice of guidelines applied in each national program depends on the country's budget for purchasing drugs, the number of TB cases to be treated, the population to be covered by the health services, the population's accessibility to these services, and the qualifications of the nearest health care staff.

- The chemotherapy regimen for each individual patient depends on the diagnostic category to which he belongs. The most contagious cases must receive four or five drugs during the initial phase of the treatment in order to reduce the risk of failure linked to a bacterial resistance (primary or acquired). (references: WHO/TB/97.220)

- For cases in Category I (new smear-positive pulmonary TB cases and severe forms of the disease), the first phase of treatment lasts two months and consists of the association of four drugs: isoniazid, rifampicin, pyrazinamide, and streptomycin (or ethambutol) given under direct observation every day or three times per week. During the continuation phase, two drugs are given for four months: isoniazid and rifampicin, every day or three times per week, or for six months: isoniazid and ethambutol (or thioacetazone) every day.

- For cases in Category II (cases that have already been treated and which need to receive re-treatment for eight months because they continue to excrete bacilli: failure or relapse after an initial treatment, continuation of treatment after a premature interruption), the initial course of treatment lasts three months and consists of the combination of four drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol, with a streptomycin supplement for only the first two months. The continuation phase lasts

five months and consists of administering three drugs: isoniazid, rifampicin, and ethambutol, given every day or three times per week under direct observation.

- For cases in Category III (new cases of primary infection and common forms of extra-pulmonary tuberculosis, new cases of limited extent, smear negative pulmonary tuberculosis), the appropriate regimen is similar to that of Category I, with the exception of the fourth drug (streptomycin or ethambutol) which should not be given during the initial phase.

  During this initial course, the three essential drugs are given: isoniazid, rifampicin, and pyrazinamide, every day or three times per week for two months. The continuation phase lasts four or six months, depending on the chosen combination of drugs.

- For the chronic cases of Category IV (smear positive pulmonary TB cases after completely supervised re-treatment), general treatment principles have been recommended by WHO for the use of second line reserve drugs in specialized centers. (reference: WHO/TB/96.210 rev. 1)

4.2 Applicability to developing country settings

4.2.1 The **proposed regimens** are applicable to all situations encountered in developing countries with a high tuberculosis prevalence at the primary health care level (with the exception of the treatment of chronic cases). They do not require an initial susceptibility test to the antibiotics. The initial phase of treatment of contagious cases (Categories I and II) must always be completely supervised, every day or three times per week, at home, at the dispensary, or at the hospital, depending on local facilities, available personnel, and the distance to be traveled by the patient or by the health care personnel for cases treated outside of the hospital. During the continuation phase (and sometimes even during the initial phase of treatment) the administering of the drugs may be supervised by a community health worker or local volunteer, provided that these individuals be trained and strictly supervised by qualified health care personnel.

4.2.2 Local **adaptations of the regimens**, the means of administering, and the methods of supervision (for "directly observed treatment", DOT) may be foreseen for patients living in particular situations:

- patients with mental illness, drug addiction, alcoholism
- prisoners, refugees living in camps
- nomads and semi-nomads, seasonal migrant workers

4.3 Applicability by level of health facility

The distribution of standardized chemotherapy regimens in each national program does not require a different level of competence for each level of health care structure, but rather demands precise organization of the internal supply and distribution of drugs, management of the stock of drugs, and supervision of the efficacy of treatment by periodic bacteriological examinations. All health care personnel in health care centers and health posts, as well as those of the local hospital and the local reference center are capable of distributing drugs to the patients, who would take them either under direct observation for the initial phase of the treatment or who would be given a supply of drugs for one, two, or four weeks during the continuation phase. In order to do this, the staff must be trained beforehand, regularly paid, and supervised. In well-organized programs, based on complete integration at the local health care level, the distribution of drugs can be decentralized to the community level, under the control of qualified health care personnel, if needed. But the volunteers or local health committees cannot substitute for health care personnel or health services deficiencies in the application or the supervision of treatment.

4.3.1 At the **pre-primary care level** (families, communities), the trained members of the community, local health care agents, or volunteers under contract must:

- encourage diagnosed patients to regularly follow the prescribed treatment
- control the BCG vaccination of children in contact with the patients
- detect abnormal symptoms appearing during the course of the treatment and immediately refer cases of hypersensitivity, jaundice, etc.
- under the authority and control of health care personnel, potentially distribute drugs to be taken under their direct supervision

4.3.2 At the **level of health posts and health centers without laboratories**, health care personnel must:

- ensure patient education
- supervise the application of prescribed treatment and regularly update the patient's chart
- gather and send sputum samples to the laboratory at specified intervals called for in the course of treatment
- trace out irregular or absent patients (with the help of health care personnel in nearby stations, community health workers, volunteers, or family tutors)

- recognize undesirable effects of the treatments

- organize contact tracing and subsequent examination

- refer all problems (medical, social, psychological) that they cannot solve, to the district level

4.3.3 At the **level of health facilities with multi-purpose laboratories** at their disposal, or/and at district level, in addition to the preceding tasks, the health care personnel must:

- ensure the bacteriological control examinations of all cases that were initially smear positive

- ensure the monitoring of treatment for each individual patient in conjunction with surrounding health care facilities

- manage of the transfer in/out and complete the forms for transfer in/out

- ensure the management of anti-TB drug stocks for registered patients

- regularly fill out and update the tuberculosis register for the district, by comparing it with the data gathered in the laboratory register

- treat the undesirable effects of specific chemotherapy

- record the results of treatment for each individual patient in the district's tuberculosis register

- fill out quarterly reports on the results of treatment for infectious cases and on the management of the program (drug consumption), and send them to their supervisors

4.4 Cost-effectiveness of treatment options

Among all of the possible health care interventions for diseases most frequently encountered, short-course chemotherapy for tuberculosis (six or eight month regimes) is the most cost-effective, provided that it is supervised on-site to reduce premature interruptions of the treatment. Whenever possible, ambulatory treatment or treatment at home must be preferred over institutional treatment, and administering drugs by mouth must be preferred to regimens requiring intra-muscular injections of streptomycin every day or three times per week.

Except for the chronic patients in Category IV, the cost of drugs in the different regimens of chemotherapy is not an obstacle for the generalization of short-course chemotherapy regimens. Even in countries with a high prevalence of tuberculosis, the cost of these anti-TB drugs only represents a small proportion of the overall pharmaceutical consumption, or 5-15 US cents per capita. In contrast, the costs of treatment for the health services (hospitalization of certain cases, personnel salaries) and for the patients (travel expenses, lost wages for hours not worked) are much higher. The decentralization of treatment for tuberculosis and its integration into the other activities of the health care personnel, responsible for applying the minimum package of health care activities to the area, reduce these costs and potentially maximize the effects of treatment.

4.5 Indicators for monitoring process and outcomes of treatment

4.5.1 To measure the performance achieved during the course of treatment as well as the final outcomes of treatment, several indicators need to be collected. For this purpose, five information sources need to be consulted in each district:

- the tuberculosis treatment register, in each health facility where many TB patients are treated;
- the treatment cards (for individual patients);
- the register of laboratory in every laboratory (multi-purpose or specialized) where microscopy for tuberculosis is performed;
- the district tuberculosis register in which the follow up and the outcome of treatment for all identified tuberculosis cases are recorded;
- the form of antituberculosis drugs stock management.

4.5.2 *At the peripheral level,* in the health facilities where TB patients are treated, a tool of management is essential to facilitate the supervisory visit. Two solutions are equally acceptable:

(a) if the number of TB patients under treatment is low (e.g. less than 10) a "TB treatment box", containing the treatment cards of individual patients is sufficient;

(b) if the number of TB patients under treatment is higher than 10 a "TB treatment register" (at health post or health center) is recommended. In this register, all the TB patients are chronologically recorded according to their TB district register number, name, age, sex and precise address. Other important information are also recorded: category of treatment initially prescribed, place of treatment during the initial phase; appointment dates for drug delivery during the continuation phase; dates (and results) of smear examinations during the treatment 2nd (3rd) month,

4th or 5th, last month; outcome explanation for death, interruption, or completed treatment.

This "TB treatment register" is a check list of all treatment cards of individual patients.

The comparison of the outpatient register (where TB suspects are recorded), the laboratory register, the TB district register and the TB treatment register (and/or individual tratment cards) allows to measure the compliance both of patients and health workers during the treatment.

The main indicators (calculated especially for the smear positive cases) for monitoring the process are:

- the proportion of TB patients who started treatment among all TB patients diagnosed;
- the proportion of TB patients sent for smear examinations and checked for AFB at 2nd –3rd month, 4th-5th month, last month among all TB patients who started treatment;
- the proportion of TB patients who completed treatment among all TB patients who started treatment.

4.5.3 *At district level*, where the district tuberculosis register and the TB laboratory register are kept and the antituberculosis drugs stock is managed, other indicators can be calculated to assess the outcomes of treatment, primarily for smear positive cases, the application of DOT, and the drug consumption.

4.5.3.1 Indicator of effectiveness of treatment during the initial phase.

This is the cumulated *rate of conversion* at two months, then at three months, for smear positive cases recorded during a quarter (new cases, relapses, and other cases in re-treatment). This rate must be at least 85% for the new cases and the relapses. It must reach at least 80% for the other cases in re-treatment.

4.5.3.2.Indicators for treatment outcomes

These indicators are provided by the analysis of cohorts of smear positive pulmonary TB cases recorded consecutively during a quarter or a year, and the available results of treatment one year following the date recorded.

Two cohorts are analyzed separately:

- the new smear positive cases

- the smear positive cases which have received standardized re-treatment (relapses, failures, and treatment after interruption)

These indicators are as follows:

- the *rate of cure*, found by the negativity of bacteriological tests over the course of the last month of treatment, as well as at another date over the course of treatment. This rate must reach at least 85%.

- the *rate of completion of treatment*, which corresponds to the proportion of patients who have finished their treatment without a bacteriological control test.

- the *rate of failure* of treatment, found by the persistence of bacilli in patients' sputum at five months of treatment or more.

- the *rate of mortality* (for any cause) over the course of treatment. Early mortality is often related to the seriousness of the disease and to delayed diagnosis.

- the *rate of interruption* of treatment, which corresponds to the proportion of patients who have interrupted their treatment for two months or more.

- the rate of transfer out, which corresponds to the proportion of patients who have been transferred to another district.

In the cohort analysis, the denominator consists of all the smear positive cases recorded (except those for which the initial diagnosis was incorrect or has been changed). Each of the rates has a particular meaning and suggests corrective measures if the rate of cure does not reach 85%. Patients who have been recorded but who have not yet begun treatment belong in the group for "interruptions" before treatment. For the purposes of evaluating the program, the *rate of success* may be measured by adding the *rate of cure* and the *rate of completion* of treatment, provided that the latter only represents a small proportion of the total.

4.5.3.3.Indicator for the rate of application of the directly observed treatment (DOT)

- the proportion of smear positive cases receiving DOT (according to the recommended national TB programme's adaptation in relation to the total recorded smear positive cases. This rate must be higher than 80%.

- among smear positive cases receiving the DOT, a distribution (expressed as a percentage) of the cases supervised by health care personnel, community health workers, or a member of their family, respectively.

4.5.3.4. Indicator for management of the anti-TB drug stock

- proportion of each type/formulation of drug consumed during a quarter in relation to the provisions for consumption for the same quarter.

4.6 Integration into minimum package of PHC activities

4.6.1 At the present time, **TB treatment activities are rarely incorporated** into the minimum package of health care activities in health care structures. Things are run as if specialized health care personnel should step in for several months and handle the prescription and distribution of the essential drugs for this disease, for which the treatment is already perfectly laid out and standardized. At the same time, however, it is considered perfectly normal to allow "generalists," either doctors or nurses, to manage 50 to 100 essential drugs for common diseases, communicable or not, that vary from diarrheal diseases to acute respiratory infections, diabetes, and high blood pressure. This attitude echoes a call for social segregation, a sentence tuberculosis has been serving since the days of the sanatorium.

In several developing countries, ambulatory treatment of tuberculosis has been decentralized and reaches as far as possible into the outlying areas, based on progress made in training health care personnel and establishing a system for supervision.

4.6.2 The aspects of treatment which may be incorporated are the following:

- the distribution of anti-TB drugs in all health centers and posts to all patients who have been diagnosed and recorded in the district.

- the bacteriological examination of sputum at fixed dates over the course of treatment, in multi-purpose laboratories in the district, which undergo quality control inspections.

- the management of the essential anti-TB drugs at the district level, the same as for other essential drugs.

4.6.3 List of the necessary means for intervention

- *Essential drugs*: Isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol (thioacetazone).

  Their use may be facilitated by *the use of fixed dose combination* of two drugs (isoniazid plus rifampicin, isoniazid plus ethambutol, isoniazid plus thioacetazone),

three drugs (isoniazid plus rifampicin plus pyrazinamide), or even four drugs (isoniazid plus rifampicin plus pyrazinamide plus ethambutol); or by presenting the drugs (alone or combined) in blisters.

- *Equipment*: When blisters are not available, zip-lock plastic bags, or containers with screw-on tops should facilitate the distribution and prevent deterioration of drug supplies for a limited period, preferably for less than one month.

  Disposable syringes and needles (if possible). Sterilization tools are mandatory equipment if disposable syringes and needles are not available.

- *Training and informational support documents* consist of technical manuals for the national TB programs, district TB registers, TB treatment center registers, individual patient cards, and quarterly reports on treatment results and drug stocks (with detailed instructions for use), drug supply forms and patient education material.

4.7 The role of the private sector

4.7.1 The **non-profit private sector** (NGOs, missions, mutual insurance companies, and dispensaries governed by a health insurance system or a company and contracted by the national anti-TB program) may be fully involved in the activities of diagnosing patients, distributing free drugs to patients, and, if necessary, in the bacteriological testing of patients over the course of treatment.

4.7.2 The **for-profit private sector** may be involved in the application of TB treatment on the basis of a contract with the public authorities, specifying that the definition of the cases, the prescribed regimens, the recording of cases, and the results of treatment are in accordance with the methods applied in the public sector, in exchange for easy access to a quality-controlled microscopic laboratory and the possible delivery of anti-TB drugs at the cost price for private structures under contract.

5. PREVENTION

5.1 The goal of health education in schools (or for mothers) is:

- to promote the BCG vaccine, integrated into the expanded programme of immunization;

- to inform the general population of the symptoms of tuberculosis (like for other respiratory diseases) and of the resources available in health care services.

5.2 The goal of health education for patients and their families is:

- to explain the contagiousness of the disease and how to prevent or limit it.

- to stress the importance of regular treatments for the patient and for those around him.

- to demonstrate the availability and willingness of the health care personnel to respond to all of the problems encountered by the patients in the course of treatment.

5.3 The **BCG Vaccine for Newborns** and for young children is the mass prevention method which must be maintained as part of the expanded programme of immunization in countries with a high prevalence of tuberculosis. Its primary purpose is to reduce the risk of severe post-primary tuberculosis in children (meningitis, miliary tuberculosis, progressive primary tuberculosis).

5.4 **Preventive Chemotherapy** only has limited individual applications. It consists of administering isoniazid alone for six months to the following categories of patients:

- apparently healthy children under five years of age, living in contact with a source of infection.

- immuno-deficient adults (with HIV or taking a long-term drug prescription), provided that the existence of active tuberculosis has first been ruled out for the individual.

5.5 **Specific Methods of Prevention** must be applied in health care services frequented by TB patients:

- *health care personnel*, especially those working in the rooms for bronchial endoscopy, dental consultations, and ear, nose, and throat consultations.

- *laboratory personnel* (use of masks and especially safety rooms when handling dangerous materials).

- *ventilation* in the hospital rooms and in the consultation rooms (and in laboratories outside of work hours).

- use of *ultra-violent lamps* to kill the bacilli that have disseminated in the area.

5.6. The best strategy for prevention remains the **Detection and Cure** of the sources of infection in the community.

6. OPERATIONAL ASPECTS

6.1 It has been proven that the integration of anti-TB activities into the general health care services would be at least as effective as having them in ***"vertical"*** programs based on specialized services. Moreover, in developing countries, the integration of these activities is the only effective method of consistently covering the most patients possible.

6.2 The advantages of a symptomatic approach for taking joint control of tuberculosis and prevailing respiratory diseases remain to be shown. We cannot be certain that by broadening the field of knowledge for health care personnel who are responsible for primary health care, the rate of detection and cure of tuberculosis will increase significantly in all countries. Again, it remains to be shown.

It is logical to think that we can increase the population's confidence in the health care services (and their use of these services, and therefore increase care and treatment). We can also reduce the number of useless trips made by the patients to be diagnosed and treated by a "specialist" in the district, the region, or the private sector (and thereby improve the patient's comfort and reduce the costs to the family's budget).

This is why studies must necessarily be multi-disciplinary and combine the economic, sociological, and psychological approaches to public health care in order to accurately evaluate the advantages of integrated management of tuberculosis and prevalent respiratory diseases into the minimum package of health care activities at district level.

6.3 There remains the difficult problem of countries where the absence of programs (or the application of obsolete programs) has caused the number of multidrug resistant TB cases to multiply over the last 10 years.

In poor countries, the care of such patients and the safety of those around them cannot be ensured. The only solution is to immediately apply a revised anti-TB program, with the goal of preventing the appearance of new multidrug resistant TB cases.

In middle-income countries, operational research should be done to choose the most effective methods for caring for patients, by combining institutional treatment and ambulatory treatment in a way that is acceptable to the patients and financially sustainable by the community and such that it offers the best chances for success.