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Consensus Statement

National Plan for the Prevention and Control of Tuberculosis in Spain[a,b]

Plan para la prevención y control de la tuberculosis en España

Tuberculosis Working Group Incorporating Scientific Societies, Autonomous Communities, and the Ministry of Health and Consumer Affairs

Introduction

Tuberculosis (TB) is a major public health problem. According to EuroTB data collected from 32 countries (the European Union plus Eastern Europe), the mean TB notification rate in 2005 was 18 cases per 100 000 population, with less than 10 cases per 100 000 in 15 countries and more than 25 per 100 000 in 6 countries.[1]

According to data provided by the Spanish epidemiological surveillance institute—the Red Nacional de Vigilancia Epidemiológica (RENAVE)—the overall TB rate for Spain in 2005 was 18.02 cases per 100 000 population, of which 15.83 cases per 100 000 were pulmonary TB. According to data published by the national notifiable diseases surveillance system (Sistema de Enfermedades de Declaración Obligatoria [EDO]) and the national microbiological monitoring system (Sistema de Información Microbiológica), respiratory TB in Spain followed a downward trend between 1999 and 2004 since when rates have tended to stabilize. TB rates vary widely across the different Autonomous Communities in Spain, although there has been a marked improvement in TB reporting in recent years. Underreporting may, however, still be widespread as the World Health Organization (WHO) estimated the overall incidence of TB in Spain to be 27 cases per 100 000 population in 2005.[1,2]

In January 2007, the Spanish department of public health (Dirección General de Salud Pública) formed a working group composed of representatives of all the Autonomous Communities to review the status of the national TB control program. That meeting highlighted the fact that the TB control programs across the country were at different stages of development and that there were marked differences between them in certain respects.

In June 2007, another working group was set up in collaboration with the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). The participants in this case were the scientific societies involved in the control of TB, the Instituto de Salud Carlos III, and representatives of some autonomous communities. The task undertaken by this group was to propose a basic set of criteria that should be met by all current and future TB control programs in Spain in each of the following areas: *a)* early detection and diagnosis; *b)* treatment; *c)* surveillance; and *d)* contact investigations.

Early Detection And Diagnosis Of Tuberculous Disease[3-8]

There is currently considerable delay in diagnosing TB, and the reduction of this delay to less than 1 month is considered a priority. One of the measures considered essential in this respect is the implementation of programs to increase awareness of TB among both primary care professionals and the general population.

A protocol should be drawn up specifying the appropriate isolation measures for each case of TB.

The basic guidelines for the early detection and diagnosis of tuberculous disease are discussed below.

Search for Cases of Tuberculous Disease

1. All persons who of their own accord seek medical advice because of an otherwise unexplained productive or unproductive cough lasting more than 2 weeks should be evaluated for TB.
2. The index of clinical suspicion for active TB should be higher in populations known to be particularly at risk for this disease.
3. Contacts of patients with tuberculous disease (particularly those who are smear positive) should be screened for TB.

Diagnostic Tests Required in All Persons With Suspected Tuberculous Disease

The standard techniques used to diagnose tuberculous disease are chest radiography and bacteriology. In certain cases, such as the diagnosis of children, the tuberculin skin test can also provide important information. All those suspected of having active disease should undergo the appropriate tests within 48 hours.

The health authorities must facilitate access to these tests (chest radiography, smear microscopy, and tuberculin skin test) within the appropriate time frame at all levels of the health care system.

[a] Document approved by the Comisión de Salud Pública del Consejo Interterritorial del Sistema Nacional de Salud (the Public Health Commission of the Regional Board of the National Health Authority) on November 15, 2007, and by the Consejo Interterritorial del Sistema Nacional de Salud (Regional Board of the National Heath Authority) on June 18, 2008.

[b] Published simultaneously in SEMERGEN. 2009;35(3):131-7.

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Chest Radiography

Chest radiography plays a key role in the diagnosis of tuberculous disease despite the fact that there is no pathognomonic sign for this disease. A normal chest radiograph rules out TB in over 95% of immunocompetent adults. Although highly sensitive, chest radiography is not a very specific test for TB and additional tests are required to confirm the diagnosis.

Bacteriology

1. *Serial sputum smear microscopy*. Smear microscopy is the simplest, least expensive, and most rapid technique for providing the clinician with a preliminary diagnostic indication. At least 3 specimens must be collected over 3 different days. Since the diagnosis of tuberculous disease is subsequently confirmed in over 95% of patients with suspected TB and a positive sputum smear, treatment should be started immediately in all patients whose sputum tests positive. However, while smear microscopy is a highly specific test, its sensitivity is only moderate (between 22% and 80% depending on clinical presentation and site of disease). This means that tuberculous disease cannot be ruled out in smear-negative patients.
2. *Culture of sputum and other clinical samples.* All specimens obtained must also be cultured because this is a more sensitive and specific technique and one that also facilitates identification of the causative organism and its susceptibility to different types of antimicrobial agents.
   The yield of sputum for both smear microscopy and culture is lower in children, and particularly in infants under 5 years of age. In young children, alternative specimens can be obtained, such as gastric lavage, or lymph node or other biopsy material.
   Since culture requires more time (up to 6 or 8 weeks) than smear microscopy, treatment should be started immediately if the patient's smear test is positive.
3. *Species identification.* The mycobacterial species isolated must be identified in all positive cultures.
4. *Susceptibility to antimicrobial agents.* All positive cultures must be routinely tested for susceptibility to first-line antibiotics (isoniazid, rifampicin, streptomycin, ethambutol, and pyrazinamide).

With the methods generally used it takes at least 2 to 4 weeks to test susceptibility even when a liquid medium is used. The results of drug susceptibility testing should be interpreted with great caution.

Techniques also exist for testing susceptibility to second-line drugs, but the results are difficult to interpret in many cases and these tests should only be carried out by reference laboratories.

Histology of Biopsy Specimens

The presence of caseating granulomas is highly sensitive and specific for the diagnosis of TB and justifies start of treatment. In cases of suspected TB, microbiological culture must be carried out to confirm the diagnosis.

Tuberculin Skin Test

The results of a tuberculin skin test should never be the sole diagnostic criteria. This technique should be complemented, if necessary, by chest radiography, smear microscopy, and culture. Tuberculin skin testing should be used to screen populations with the highest probability of tuberculous infection or disease, such as children with suspected TB and the close contacts of smear-positive patients. Tuberculin skin testing is not generally recommended in low-risk groups because of the high rate of false positives that occurs in such populations. The results of tuberculin testing must be interpreted in accordance with the official international guidelines.

Other Diagnostic Techniques

Techniques that detect the nucleic acid found in microorganisms of the *Mycobacterium tuberculosis* complex in clinical specimens can, when available, be used to support diagnosis. The results of these assays should be evaluated in conjunction with the clinical findings and the results of other diagnostic tests.

Measurement of interferon gamma using the whole blood interferon-γ release assay has been shown to be as sensitive and specific as tuberculin skin testing for the diagnosis of tuberculous infection. However, systematic guidelines for the use of this assay have not yet been developed.

All patients diagnosed with active TB should be offered the possibility of being tested for the human immunodeficiency virus (HIV).

Treatment Of Tuberculous Disease[5,6,8,9]

Correct treatment is the best measure for controlling TB. Free treatment must be offered to all patients with TB in Spain.

Treatment

Patients Never Previously Treated for TB (New Cases)

New cases of TB should be treated with a combination of first-line antituberculosis drugs for an appropriate period of time; the drugs should be administered simultaneously in a single dose. The standard initial course of treatment that should be used in all patients when no contraindication exists to any of the component drugs is 2 months of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E); the continuation phase of treatment should be 4 months of H and R (2HRZE+4HR).

It is, however, possible that the same regimen without E may still be valid in the autonomous communities where the overall rate of resistance to H is under 4%.

Children generally present good tolerance to treatment and should, therefore, be treated with the regimen recommended for adults, adjusting the pharmacological dose to the child's body weight. The dose of E in children, and particularly in those under 5 years of age, should never exceed 20 mg/kg/d; the recommended dose is 15 mg/kg/d. The WHO recommends a daily dose of H for children of 5 mg/kg (range, 4-6 mg/kg) and a maximum daily dose of 300 mg.

The use of fixed-dose combinations is recommended. The following fixed-dose combinations are currently available in Spain: 4 drugs (RHZE), 3 drugs (RHZ), and 2 drugs (RH).

All TB programs must include a subprogram for directly observed treatment (DOT). DOT must be prescribed in all patients who are likely, because of their personal or social situation, to find it difficult to complete the treatment regimen (homeless persons, prisoners, drug addicts, etc), and in patients with multidrug resistant or extensively drug resistant TB.

In special clinical situations, such as tuberculous meningitis, liver or kidney disease, pregnancy, or HIV infection, it may be necessary to modify the treatment regimen, and this should be done by a specialist.

Treatment failure—when the standard regimen does not result in a negative culture after 4 months of treatment—may indicate nonadherence to treatment or the presence of drug-resistant strains. These cases must be assessed by physicians with specific expertise.

Patients Previously Treated for TB (Retreatment)

All patients who have received prior treatment for TB must be treated and monitored by designated medical professionals with specific expertise in TB. These specialists must be designated in each autonomous community.

Follow-up

The objective of monitoring treatment is to ensure adherence to treatment and to assess efficacy, as well as to identify and manage the side effects of antituberculosis therapy.

A fixed number of appointments must be arranged and the patient must attend. Follow-up should consist of at least 5 visits: 15 days, 1 month, 2 months, 4 months, and 6 months after start of treatment. Health care professionals and the public health services should monitor this process to ensure that the patient attends all appointments and must contact all patients who fail to attend.

Any bacteriological, clinical, analytical, and radiographic tests considered necessary should be carried out at each of these visits. The clinical team should also encourage the patients to complete the full course of treatment.

The treatment regimen followed by each patient must be recorded together with the results of all the tests carried out and the final outcome.

A protocol should be drawn up to define the legal basis for the implementation of special public health measures when a patient refuses to take antituberculosis treatment.

Treatment Outcome Monitoring

It is important to record final treatment outcomes using the definitions established by the international bodies. These definitions are included in the protocol drawn up by RENAVE, the Spanish national epidemiological surveillance body.

Surveillance Of Tuberculous Disease[10-14]

TB surveillance in Spain is regulated by Real Decreto 2210/1995, an act initially drafted by RENAVE and subsequently developed in the EDO protocols and the specific legislation of each autonomous community.

To improve TB control, the current surveillance system must be improved by establishing a national register. This register will make it possible to improve the collection and analysis of data in the event of new cases and outbreaks, will include microbiological information about resistance, and will bring together the data currently held on several different systems.

TB Case Definition

The TB case definition currently in use can be found in the surveillance protocol available online (http://www.isciii.es/htdocs/centros/epidemiologia/procedimientos/modificacion-protocolo-TBC.pdf).

The new definition proposed by the European Center for Disease Prevention and Control is as follows:

Clinical Criteria

Any person who fulfills both the following criteria is considered to be a TB case:

1. Signs, symptoms, and/or radiological findings consistent with active TB in any site.
2. Prescription of a full course of antituberculosis therapy

Or:

A case discovered post-mortem with pathological findings consistent with active TB that would have indicated antituberculosis treatment had the patient been diagnosed before death.

Laboratory Criteria

1. Criteria for a confirmed case:
   At least 1 of the following 2 criteria:
   - Isolation of a microorganism of the *M tuberculosis* complex (excluding *Mycobacterium bovis*—BCG) from a culture of a clinical specimen.
   - Detection of *M tuberculosis* complex nucleic acid in a clinical specimen.
     And observation of acid-fast bacilli using microscopy or an equivalent technique.
2. Criteria for a probable case:
   At least 1 of the following 3 criteria:
   - Observation of acid-fast bacilli using microscopy or an equivalent technique.
   - Detection of *M tuberculosis* complex nucleic acid in a clinical specimen.
   - Histological appearance of granulomas.

Classification of Cases

1. Possible or suspected case**:** any case fulfilling the clinical criteria
2. Probable cases: any case fulfilling the clinical criteria plus the laboratory criteria for probable cases
3. Confirmed cases: any case fulfilling the clinical criteria plus the laboratory criteria for confirmed cases

The definitions for new cases, previously treated cases, pulmonary TB (smear-positive and smear-negative), and extrapulmonary TB are given in the surveillance protocol cited above. A definition is needed for imported cases.

Criteria will be drawn up for the definition and notification of imported cases following the guidelines of the European surveillance network.

Notification of TB Cases

Notification is mandatory for all cases of TB fulfilling any 1 of the 3 definitions of suspected, probable, or confirmed TB.

Previously treated cases should not be reported again until at least 12 months have elapsed since the last time the patient completed a full course of antituberculosis treatment.

The medical professional must notify the appropriate authorities as soon as possible and never later than 1 week after diagnosis, especially in the case of infectious patients.

In order to obtain a centralized database of case-by-case data, all new cases must be included in the national TB register.

Essential Specific Variables for Which Data Must Be Obtained in All Cases of TB

In addition to the standard variables recorded for all diseases subject to mandatory reporting (age, sex, autonomous community, week of notification, etc), the following specific variables must also be reported:

1. Case classification (suspected, probable, or confirmed)
2. Date of starting treatment
3. Date of onset of symptoms
4. Country of origin of the patient (country of birth)
5. Date of arrival in Spain

6. Type of case by treatment history (new or previously treated)
7. Principal site of disease (pulmonary, pleural, lymphatic, bones and joints, tuberculous meningitis, central nervous system other than tuberculous meningitis, genitourinary, digestive tract, disseminated, and other sites)
8. Additional site of disease, if applicable
9. Smear test results (positive, negative, not carried out, result unknown)
10. Culture results (positive, negative, not carried out, result unknown)
11. Identification of microorganism isolated (*M tuberculosis, M bovis, Mycobacterium africanum, M tuberculosis* complex, *Mycobacterium caneti,* not identified)
12. Other tests (histology—positive, negative, none carried out, result not known; nucleic acid detection—positive, negative, not carried out, unknown)
13. Drug combination prescribed (isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin, others) and treatment regimen
14. Antibiogram (carried out, not carried out, result unknown)
15. Resistance to any of the 5 first-line drugs (yes, specify; no, unknown)
16. Presence of HIV antibodies (yes, no, not tested, result unknown)
17. Contact investigation (yes, no, not indicated, impossible, unknown)
18. Treatment outcome (cure, treatment completed, failure, transfer out, treatment default, death as a result of TB, death from other causes, other, not assessed, treatment prolonged because of complications, initial regimen prolonged for more than 12 months, no information available)

Treatment Outcome Categories

Follow-up on outcomes 12 months after start of treatment is reported using the 7 standardized and mutually exclusive categories defined in the current surveillance protocol.

Collection of this information is very important on both the local and the national level because treatment outcomes can be used as an indicator to evaluate the quality and impact of TB control programs.

This information must be routinely updated in the register by the health care professionals.

A protocol for TB surveillance, follow-up, and treatment outcome monitoring will be drawn up.

Surveillance of TB Outbreaks

Epidemiological surveillance of TB outbreaks can be used to evaluate the effectiveness of the control measures implemented and provides useful data concerning transmission mechanisms. The current surveillance protocol defines an outbreak as the appearance of 1 or more cases of TB related to the first detected case and stipulates the notification procedure.

All outbreaks must be reported to the local health authorities and, within 3 months of the end of the outbreak, a report providing further information must be submitted to the national authorities. Data on outbreaks will be updated periodically on a national level.

Since any case of TB affecting a child may indicate the existence of an outbreak, an appropriate investigation must be undertaken in all such cases.

Molecular epidemiology techniques provide essential genetic information for the study of outbreaks. They are also very useful for ruling out false positives caused by contamination of laboratory specimens and other circumstances. Coordinated use of such techniques is useful for the identification of highly infectious strains, for completing and validating contact investigations in the population, and for the study of multidrug-resistant strains.

Given the fact that TB outbreaks have unique characteristics that distinguish them from outbreaks of other diseases subject to mandatory reporting to the national surveillance network, specific criteria will be drawn up for the surveillance and notification of this disease.

Surveillance of Antimicrobial Resistance

Surveillance of resistant and multidrug resistant TB strains is useful for assessing and improving case management, contributes to the identification of vulnerable groups, and provides useful information on transmission.

Routine collection of the following data on a national level is considered necessary: the results of antituberculosis drug susceptibility tests for all strains from patients with in cases of active disease, including data on both susceptible and resistant strains. This task should be carried out by the corresponding reference laboratory, as recommended by the international bodies.

Since 1998, a group of laboratories have voluntarily participated in a study of multidrug-resistant strains based on the use of epidemiological markers. The results of this study are stored in a database of the restriction fragment length polymorphism patterns of the multidrug-resistant strains isolated.

A national network of laboratories should be developed. The following data should be included in the TB case register: information on the results of antibiotic susceptibility testing and, whenever possible, on the genetic pattern of the strains isolated together with the clinical and epidemiological characteristics of the associated TB case.

Active Case Search

In addition to TB surveillance by way of mandatory reporting and in order to identify cases not detected by this system, cases of TB should be actively sought using other complementary sources, such as bacteriology services, hospital admissions data, acquired immunodeficiency syndrome (AIDS) records, death certificates, and data from correctional facilities, among others. Before notifying the national epidemiological institution (Centro Nacional de Epidemiología) of any unreported cases, the information obtained from these sources should be cross checked on a local level to avoid duplicate notification.

Surveillance Indicators

Given that the primary aim of surveillance is to monitor trends over time, the indicators used must be valid, comparable, and operative.

A set of indicators for assessing TB control programs will be defined.

The information obtained in 2007 about TB cases will be used to establish a baseline, thereby making it possible to fix objectives for the prevention and control plan.

Contact Investigations[6-8,15]

All TB control programs must refine and expand their contact tracing activities because additional cases of TB infection or disease may be found among the contacts of every index case.

In countries with sufficient health resources, such as Spain, a contact investigation must be carried out for every case of TB diagnosed. Smear-positive and culture-positive cases of pulmonary TB are the highest priority. The contacts of patients under 15 years of age with a positive tuberculin skin test result should also be studied to identify the source of infection, and likewise the contacts of individuals whose skin test result has recently become positive.

Requirements for Contact Investigations

1. TB programs must include contact investigations that extend beyond the immediate family and also take into account workplace and school contacts.
2. Investigations should be carried out using the concentric circle method, with priorities being established on the basis of the likelihood of TB infection and the potential outcome of such infection. Investigation of the contacts of smear-positive patients is a high priority.
   Priorities in contact tracing:
   – High priority contacts: *a)* close contacts and persons in prolonged contact with index cases (>6 hours a day); *b)* children under 5 years of age; and *c)* immunocompromised contacts
   – Medium priority contacts: persons in daily contact with the index case, but for less than 6 hours a day
   – Low priority contacts: casual contacts (not daily)
3. All health care centers should be informed of the names of the designated expert professionals for the management of TB cases in their area. The public health service will coordinate contact investigations in both the health care setting and in close-knit or closed communities.
4. The contacts of each index case will be studied and followed up to identify individuals with TB infection or active disease and the real index cases; a review of the investigation should be carried out within 1 week of the diagnosis of the first case. The contact investigation should be started as soon as possible in order to take advantage of the impact produced by the diagnosis of TB. The highest yield is obtained among the contacts of smear-positive cases (more infectious), children, and immunocompromised individuals. However, it should not be forgotten that smear-negative cases can also give rise to infection and disease. Patients will be monitored to ensure that the treatment regimen prescribed is implemented and completed (whether chemoprophylaxis, or treatment of latent TB infection or tuberculous disease.
5. The work of all the parties involved should be coordinated; these include the medical centers carrying out the contact investigation, the heath care professionals who diagnose the TB cases, and the microbiological laboratories (including the laboratories that carry out the molecular epidemiology studies).
6. A standard form should be created for the collection of contact data. All this information should be stored on an appropriate database. The system will be evaluated annually.
7. The incorporation into the program of community health care workers who come from social and cultural environments similar to those of the patients is a very useful strategy both for locating contacts and bringing them into contact with the health service and for improving treatment adherence among patients.
8. On the basis of the information collected during the contact investigation about the domestic, social, and labor situation of patients and their contacts, the health care professionals should consider whether any of the individuals contacted would benefit from referral to the social services with a view to providing them with services of a social worker and/or legal aid to improve their living conditions. This is a way to facilitate treatment adherence and to reduce the risk of disease propagation, patient relapse, and reinfection.

Members of the Tuberculosis Expert Working Group

Scientific Societies:

Sociedad Española de Neumología y Cirugía Torácica (SEPAR)
Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC)
Sociedad Española de Medicina Preventiva, Salud Pública e Higiene (SEMPSPH)
Sociedad Española de Sanidad Penitenciaria (SESP)
Sociedad Española de Neumología Pediátrica (SENP)
Sociedad Española de Epidemiología (SEE)
Sociedad Española de Médicos de Atención Primaria (SEMERGEN)
Sociedad Española de Medicina Interna
Sociedad Española de Medicina de Familia y Comunitaria (semFYC)
Sociedad Española de Medicina de Urgencias y Emergencias
Sociedad Española de Salud Pública y Administración Sanitaria (SESPAS)

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Generalitat de Catalunya
Xunta de Galicia
Generalitat Valenciana

Ministry of Health and Consumer Affairs:

Public Health Authority:

– Centro de Coordinación de Alertas y Emergencias Sanitarias (CCAES)
– Secretaría del Plan Nacional del SIDA

Instituto de Carlos III:

– Centro Nacional de Epidemiología (CNE)
– Centro Nacional de Microbiología (CNM)

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Junta de Andalucía
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Ministry of Health and Consumer Affairs:

Department of Public Health:

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Instituto de Salud Carlos III:

– Centro Nacional de Epidemiología (CNE)
– Centro Nacional de Microbiología (CNM)

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