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Tuberculosis in Spain: An opinion paper

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ABSTRACT

This document is the result of the deliberations of the Committee on Emerging Pathogens and COVID-19 of the Illustrious Official College of Physicians of Madrid (ICOMEM) regarding the current situation of tuberculosis, particularly in Spain. We have reviewed aspects such as the evolution of its incidence, the populations currently most exposed and the health care circuits for the care of these patients in Spain. We have also discussed latent tuberculosis, the reality of extrapulmonary disease in the XXI century and the means available in daily practice for the diagnosis of both latent and active forms. The contribution of molecular biology, which has changed the perspective of this disease, was another topic of discussion. The paper tries to put into perspective both the classical drugs and their resistance figures and the availability and indications of the new ones. In addition, the reality of direct observation in the administration of antituberculosis drugs has been discussed. All this revolution is making it possible to shorten the treatment time for tuberculosis, a subject that has also been reviewed. If everything is done well, the risk of relapse of tuberculosis is small but it exists. On the other hand, many special situations have been discussed in this paper, such as tuberculosis in pediatric age and tuberculosis as a cause for concern in surgery and intensive care. The status of the BCG vaccine and its present indications as well as the future of new vaccines to achieve the old dream of eradicating this disease have been discussed. Finally, the ethical and medicolegal implications of this disease are not a minor issue and our situation in this regard has been reviewed.

Keywords: Tuberculosis, situation in Spain, diagnosis, extrapulmonary tuberculosis, latent tuberculosis, pediatric tuberculosis, incidence, populations at risk, medical-legal aspects, recurrence, vaccines, treatment, new drugs, bedaquiline, delamanid, Intensive Care Unit, microbiological diagnosis.

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Tuberculosis en España: Un documento de opinión

RESUMEN

El presente documento es el resultado de las deliberaciones del Comité sobre Patógenos Emergentes y COVID-19 del Ilustre Colegio Oficial de Médicos de Madrid (ICOMEM) en relación a la situación actual de la tuberculosis, particularmente en España. Hemos revisado aspectos tales como la evolución de su incidencia, las poblaciones actualmente más expuestas y los circuitos sanitarios para la atención a estos pacientes en España. Se ha discutido también la tuberculosis latente, la realidad de la enfermedad extrapulmonar en el siglo XXI y los medios de que en la práctica diaria se dispone para el diagnóstico tanto de las formas latentes como de las activas. La aportación de la biología molecular que ha cambiado la perspectiva de esta enfermedad ha constituido otro de los temas de debate. El documento trata de poner en perspectiva tanto los fármacos clásicos y sus cifras de resistencia como la disponibilidad e indicaciones de los nuevos. Junto a esto, se ha discutido la realidad de la observación directa en la administración de fármacos antituberculosos. Toda esta revolución está posibilitando el acortamiento del tiempo de tratamiento de la tuberculosis tema que ha sido igualmente revisado. Si todo se hace bien, el riesgo de recaída de la tuberculosis es pequeño pero existente. Por otra parte, muchas situaciones especiales han merecido discusión en este documento como por ejemplo la tuberculosis en edad pediátrica y la tuberculosis como causa de preocupación en cirugía y cuidados intensivos. Se ha discutido tanto la situación de la vacuna BCG y sus indicaciones presentes, como el futuro de nuevas vacunas que permitan alcanzar el viejo sueño de erradicar esta enfermedad. Finalmente, las implicaciones éticas y medicolegales que esta enfermedad plantea no son un tema menor y se ha revisado nuestra situación en este particular.

Palabras clave: Tuberculosis, situación en España, diagnóstico, tuberculosis extrapulmonar, tuberculosis latente, tuberculosis pediátrica, incidencia, poblaciones de riesgo, aspectos médico-legales, recidiva, vacunas, tratamiento, nuevos fármacos, bedaquilina, delamanida, Unidad de Cuidados Intensivos, diagnóstico microbiológico.

INTRODUCTION

Tuberculosis has accompanied mankind for as long as we can remember and continues to do so at the present time. The population of the economically richest countries, and some medical professionals, consider it an extinct or semi-extinguished disease of which the most basic reality is often ignored. We are talking about a disease that the World Health Organization has repeatedly failed to predict its eradication date and in which pandemics such as HIV and the great migratory phenomena have changed many aspects**.** Science, on the other hand, has been very active in this field of knowledge, with giant steps forward in the field of diagnosis, treatment and prevention.

For these and other reasons, the COVID and Emerging Pathogens Committee of the Illustrious Official College of Physicians of Madrid (ICOMEM), has asked itself about the recent state of tuberculosis in Spain and in its deliberations a series of questions have arisen to which we have tried to seek answers. On this occasion we have also turned to experts on the subject, from outside the Committee, who have helped us extraordinarily in the preparation and orientation of this document.

We will now go on to discuss the questions chosen, which we hope will be of interest to both physicians and the general public, both inside and outside our country. Nothing could be further from us than the pretension of being exhaustive and even less so in a subject such as this. As on other occasions, where scientific evidence has not been available, we have supplemented it with aspects of opinion that we wanted to share with our readers.

WHAT IS THE CURRENT SITUATION OF TUBERCULOSIS IN SPAIN IN TERMS OF NUMBERS AND WHERE HAVE WE COME FROM IN RECENT YEARS?

Tuberculosis (TB) has been a notifiable disease since the beginning of the last century. In addition, there is a special surveillance protocol for this disease approved in 2013 [1] which allows us to have updated information about it. Surveillance is a basic tool to monitor the achievements of the TB Control and Prevention Plan, developed by the Interterritorial Council of the National Health System in 2019 [2].

Based on data updated to March 2023, from the National Epidemiological Surveillance Network [3], in 2021, 3,754 TB cases were reported in Spain, of which 151 were imported. Thus, among non-imported cases (n=3,603), the notification rate (NR) was 7.61 per 100,000 population. This represents a decrease of 2.18% compared to 2020 (3,686 cases and NR=7.78) and 28.07% compared to 2015 (4,913 cases and NR=10.59). Consequently, Spain is a country with a low incidence of this disease. In addition, the first two goals of the TB Control and Prevention Plan were met in 2020 [2]. The first was to reduce the overall rate by 15%-21% in 2020 compared to 2015; and a reduction of 26.5% was achieved. The second target was to reduce the average annual rate of pulmonary TB (70% of all TB cases) by 4% in the period 2015- 2020; and a 6% reduction was achieved.

However, to achieve the end of TB, the World Health Organization (WHO) has proposed a 90% reduction in NR by 2035 compared to 2015 [4]. To achieve this, our rate would have to be reduced by 9.5% per year, a reduction greater than that observed in the 2015-2020 period, which was only 6%, and considerably higher than the 2.2% reduction recorded in 2021 with respect to 2020; therefore, if this rate of decline were to be maintained, the WHO target would not be achieved among us. The autonomous communities and cities with the highest NR in 2021 were Ceuta, Galicia, Catalonia, Rioja and the Basque Country, while those with the lowest

NR were the Canary Islands, Castilla La Mancha, Extremadura, and Navarre. And in practically all of them TB NR has decreased from 2015 to 2021.

In 2021, TB NR was always higher in men than in women (rate ratio 1.7) and was similar from 25 to 84 years of age. Almost half of the TB cases affected persons not born in Spain, and their mean age was considerably younger than that of those born in our country. It is noteworthy that 155 cases were reported in children under 15 years of age (79 in children under 5 years of age and 76 in the group aged 5 to 14 years). These figures are the lowest in the 2015-2021 period in Spain and represent a 54% decrease compared to 2015.

Of the total TB cases reported in 2021, 76.7% (n= 2,764) had information on HIV testing, with 179 (6.5%) testing positive. In 2021, 155 deaths were reported and TB mortality was 0.45 per 100,000 population. Mortality was higher in males than in females (2.6 times higher) and has followed a downward trend in the period 2015-2021.

Unfortunately, it has not been possible to assess, due to lack of adequate information (e.g., resistances), whether the two goals of the TB Control and Prevention Plan on TB treatment have been achieved; the goals were to achieve a treatment success rate of 95% for drug-sensitive cases and 75% in cases with resistances.

IS THERE CURRENTLY A POPULATION AT PARTICULAR RISK OF TUBERCULOSIS IN SPAIN?

No particular risk factors have been identified for the development of TB in Spain. However, at a global level, the National Epidemiological Surveillance Network has collected some traditional factors that could be associated with an increased risk [5]. Sex and age maintained their secular trend of higher frequency in men (male/female ratio of 1.7) and higher frequency of pulmonary forms in those over 65 years of age. However, the median age was 47 years in 2021 [3]. It does not appear, therefore, that these demographic characteristics allow the identification of any group at higher risk of the disease. There are, however, other factors that can identify a higher risk population. Coming from countries with a high incidence and prevalence of tuberculosis is undoubtedly one of these factors [3,5]. The country with the highest number of cases in the Registry was Morocco, followed by Romania, Bolivia, Peru and Pakistan [5]. It should be noted that, among this foreign population, the age at diagnosis of tuberculosis is lower (mean 39 years) and that more than half of the cases had been residing in Spain for more than 10 years and only 13% had been in Spain for less than two years. The other risk factor that continues to be recorded is HIV coinfection. The number of persons with tuberculosis who are HIV-positive has been declining and now accounts for 4.4% of the total (7% of those reported). This high frequency still makes it advisable to exclude HIV infection in persons with tuberculosis, regardless of age and presentation. Although persons with HIV present more frequently with extrapulmonary and systemic forms of tuberculosis, the majority remain pulmonary forms. Information on other risk factors (injection drug use, alcoholism, etc.) has recently been incorporated into the protocol of the National Epidemiological Surveillance Network, but data collection has still been scarce.

In summary, there is no population at particular risk of developing tuberculosis in Spain. However, coming from countries where prevalence is high and HIV infection identify two groups in which the suspicion of tuberculosis should be particularly high in the presence of a compatible clinical presentation.

IN WHICH CIRCUITS OF THE HEALTH SYSTEM ARE PATIENTS WITH TUBERCULOSIS DIAGNOSED AND TREATED IN SPAIN?

There are plans for the prevention and control of tuberculosis in Spain, both at the State and Autonomous Community levels [6]. These plans structure the strategic lines to be followed from the point of view of diagnosis and treatment, regardless of the level of care at which the patient is treated. The ultimate goal of these plans is to reduce diagnostic delay and treatment initiation, limit transmission and outbreaks, and prevent disease progression.

The symptoms of tuberculosis can be heterogeneous and non-specific, so it is very important to identify patients at risk (HIV, silicosis, poorly controlled diabetes mellitus, dialysis, transplant recipients, immunosuppressive treatment, nutritional deficiency and any condition that depresses the immune system) and socioeconomic circumstances that increase prevalence (malnutrition, poverty, overcrowding, drug addiction, migration from areas of high incidence).

Patients with suspected tuberculosis can present in any health care setting, whether primary or specialized care, so it is essential to carry out outreach sessions for health care professionals in order to make them aware of the problem that tuberculosis can pose.

The definitive diagnosis of tuberculosis is microbiological and will be carried out in laboratories with adequate facilities and will ensure that a complete diagnosis is made.

In the primary care setting, the microbiological studies necessary to establish the diagnosis can be requested, except for immunological tests, and treatment can be prescribed, although sometimes the patient is referred to specialized hospital care, mainly internal medicine, for evaluation of the situation. However, there is no protocol recommending referral to Hospital Specialized Care and it is more a personal criterion of the attending physician. On the other hand, Primary Care can carry out the contact study, focusing on the patients living with the case, and leaving the rest of the contact studies in the hands of Public Health. Patients with suspected tuberculosis are seen with some frequency in the emergency department [7], where the initial diagnostic tests may be requested and the patient may be referred to outpatient clinics or admitted depending on the patient's clinical situation.

WHAT DO WE UNDERSTAND BY LATENT TUBERCULOSIS, WHAT DOES IT REPRESENT IN SPAIN AND HOW SHOULD IT BE MANAGED?

Latent tuberculosis infection (LTBI) is defined by the presence of a state of persistent immunity to *Mycobacterium tuberculosis* in the absence of clinical manifestations of tuberculous disease. The WHO estimates that up to 30% of the world's population may develop LTBI in their lifetime, but obviously these figures vary according to the economic and social development of countries [8,9]. Thus, CDC publications estimate that 5% of the US population has LTBI. There is consensus that between 5 and 10% of people with LTBI will develop tuberculosis disease, with the risk of disease being higher in the first 5 years of primary infection and especially in children and immunocompromised individuals. There is also agreement that detection of LTBI in cases requiring treatment is essential for the prevention and control of the disease.

In countries with a low incidence of the disease (<100/100,000) and medium or high economic resources, a group in which Spain would be included, the WHO recommendations for the systematic diagnosis of LTBI and its treatment in case of confirmation, are established in two population groups [10]:

- High recommendation: patients with HIV infection, adults and children in contact with tuberculosis cases, patients who are going to start treatment with anti-TNF drugs, patients on dialysis, patients who are going to undergo bone marrow or solid organ transplantation and patients with silicosis.

Conditional referral to patients with socio-economic determinants: prisoners, healthcare workers, homeless, immigrants from high-incidence countries and drug users.

In Spain, the Strategic Plan for Tuberculosis Control, updated in 2019, adds other situations to be considered, such as aid workers and military personnel on mission in high-incidence countries, homes for the elderly, children who have traveled to high-incidence countries 10 weeks after their return, shelters for homeless people and people in immigrant care centers [11].

The strategic plan establishes among its indicators the proportion of subjects with a positive test and who are eligible for treatment and the percentage of subjects in which treatment is carried out. However, these indicators have only been reported by 5 autonomous communities and only in one of them were both percentages 100% [12].

The diagnosis of LTBI can be made by Tubercular Skin Test (TST) or interferon gamma release assays (IGRA). The comparative characteristics of the two tests are discussed elsewhere in this publication. A TST is considered positive when the induration of the papule exceeds 5 mm, although in subjects with a history of BCG vaccination the diagnosis of LTBI should be confirmed by an IGRA test [13,14].

A meta-analysis of data published up to December 2021 on the benefits and risks of screening patients with suspected LTBI has recently been conducted [9]. The paper included 113 publications but no studies directly evaluated the benefits and risks of screening. Pooled estimates of the sensitivity of the Tuberculin test (TST) were 0.80 at the 5 mm induration threshold, 0.81 at the 10 mm threshold, and 0.60 at the 15 mm induration threshold. The pooled estimates of the sensitivity of the IGRA tests ranged from 0.81 to 0.90. Overall, the pooled estimates of the specificity of the screening tests ranged from 0.95 to 0.99.

A randomized clinical trial (n = 27,830 subjects) found a relative risk of progression to active TB at 5 years after taking 24 weeks of Isoniazid (INH) of 0.35 compared to the untreated. Those treated with INH, however, had a higher risk of hepatotoxicity [9].

In LTBI prophylaxis, compared to INH monotherapy, adherence may be better with shorter combination treatments associating isoniazid with rifampicin or rifapentine. The guidelines established by the CDC in 2020 are as follows [15]:

Association of Isoniazid 300mg and Rifapentine 900 mg once a week under directly observed therapy for 3 months.

2.- Isoniazid 300mg/day plus Rifampicin 600 mg/day for 3 months.

3.- Isoniazid 300 mg/day for 6 months.

The consensus documents of the Spanish scientific societies also place the combination of rifampicin and Isoniazid in first place over Isoniazid alone [16,17] and the latest publications now include a regimen of isoniazid and rifapentine.

WHAT DO IGRAS PROVIDE AND HOW DO THEY COMPARE WITH TST IN THE DIAGNOSTIC CONTEXT?

The Mantoux tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) are diagnostic tests for *Mycobacterium tuberculosis* infection. Both rely on cellular immuno-response to mycobacterial antigens. The window period for detection ranges from 2-12 weeks, being shorter with IGRAs [18,19]. These tests cannot differentiate between a previous or current *M. tuberculosis* infection, nor between latent (LTBI) or active infection [20]. They are generally used as screening tests for LTBI in people who are at high risk of developing active tuberculosis.

The TST has been for many years the reference test used in the diagnosis of LTBI. It measures the delayed hypersensitivity reaction to a mixture of antigens common to different mycobacterial species contained in a purified protein extract (PPD). This multiple composition means that its sensitivity and specificity are not sufficiently high [18].

IGRAs were designed to complement the diagnosis of LTBI and detect the production of interferon gamma by T lymphocytes sensitized to *M. tuberculosis*, after stimulation with specific antigens [1,2]. The two main antigens used are the 6 kD *M. tuberculosis* early secretion antigenic target protein (ESAT-6) and the 10 kD culture-filtered protein (CFP-10), two strongly

Table 1 **Comparison between TST (Mantoux) and IGRAs for the detection of *Mycobacterium tuberculosis* infection.**

Features	TST	IGRAs
Antigens included in the test	Mixture of > 200 antigens of *M. tuberculosis* and other mycobacteria	2-3 types of antigens almost exclusive to *M. tuberculosis*.
Time to results	At least 48-72 hours	24 hours
Sample processing	No, in vitro performance	Yes, in vitro performance
Cross reaction	Yes, with BCG and MNT vaccination	Rare with BCG vaccination Only with some NTMs
Interference of results with recent viral infection and/or "live" virus vaccines[a]	Yes	Yes with vaccination Not clarified effects of acute infections
Window periods (mean)	2-4 weeks	8 weeks
Sensitivity	55-83%	52-94%
Booster effect[b]	Yes	No
Loss of sensibility in special populations	Yes	Yes Better performance than TST
Specificity	70-92%	90-100%
Cost	Low	Higher

NTM: nontuberculous mycobacteria; BCG: bacillus Calmette-Guérin.

[a]For example: measles, mumps, chickenpox, influenza.

[b]Positivization of previously negative TST due to tuberculin push effect in vaccinated patients or patients with decreased sensitivity to tuberculin.

immunogenic *M tuberculosis* antigens that are highly specific for *M. tuberculosis* [18,19]. However, they are not completely exclusive to *M. tuberculosis* and are also found in *M. africanun, M. bovis* (not in *M. bovis* - BCG vaccine) and in some non-tuberculous mycobacteria (*M. szulgai, M. flavescens, M. marinum* and *M. kansasii*), increasing the likelihood of false positives [18,19].

Among the main advantages of IGRAs over TST are the high specificity for the detection of *M. tuberculosis* in any type of population [20,21] and a higher sensitivity than TST [22]. They are especially useful in immunocompetent persons, older than 5 years of age [20,21,23]. Although the usefulness of this test is more limited in immunosuppressed patients, the specificity is higher than that of TST [24,25]. Despite their higher cost, IGRAs appear to be cost-effective in LTBI screening strategies in high-income settings for high-risk patients [26]. Newly developed or upgraded generations of IGRAs have shown similar diagnostic performance to older IGRAs and maintain the highest specificity relative to TST [27]. In addition, these new tests have demonstrated a good ability to rule out a diagnosis of active tuberculosis in clinical settings with a low to moderate prevalence of tuberculosis [28]. The advantages of IGRAs also include less likelihood of cross-reactivity to BCG vaccine and exposure to other non-tuberculous mycobacteria, less subjective interpretation, shorter window period, faster results, and the possibility of detecting false negative TST results due to skin anergy situations [18] (Tables 1 and 2).

For these reasons, IGRAs have now become the standard of care for detecting LTBI. In 2016 a Panel of experts from the Mycobacteria Study Group (GEIM) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Society of Respiratory Diseases and Thoracic Surgery (SEPAR), developed an evidence-based guideline on the use of IGRAs to diagnose TB infection in immunocompetent and immunocompromised adults and children of any age with risk or suspicion of active TB [29].

WHAT IS THE STATUS OF EXTRAPULMONARY TUBERCULOSIS IN THE 21ST CENTURY?

Active tuberculosis outside the lung, the organ of entry and preferred target, is a frequent presentation within the large clinical spectrum of the disease. In classical series, extrapulmonary tuberculosis (EPTB) accounted for less than 20% of cases [30, 31]. In a small percentage (1 to 2%), the disease was disseminated, with a histological and clinical appearance of "millet grain" lesion seeding (Miliary Tuberculosis (MT), which evidenced the failure of the immune response and a fatal prognosis [32].

A number of causes have led to changes in the clinical presntation of TB, with a relative increase in EPTB [33-36]. These included the emergence of HIV as an emerging disease that greatly increased the risk of developing TB with a high proportion of EPTB [37-41]. Other forms of immunosuppres-

Table 2 Recommendations for the use of IGRAs in different clinical settings

Clinical environments	Recommendation	FR	Quality
IGRA for TB patient contact tracing	The panel suggests initiating contact tracing with the TST, but in BCG-vaccinated contacts, positive TST results should be confirmed with an IGRA performed on the date of TST reading.	Weak	Low to very low
IGRA for healthcare workers	Use TST for initial and periodic screening of health care workers, but positive TST results should be confirmed with an IGRA performed on the reading date. If TST becomes positive and IGRA remains negative, perform periodic screening with IGRA only if there is no suspicion of active disease or evidence of immunosuppression.	Weak	Moderate (IGRA) Very low (TST)
IGRAs for the diagnosis of active TB in children < 5 years old	In < 5 years with suspected active TB, the panel suggests using both TST and an IGRA to complement microbiological and radiographic studies for the diagnosis of active TB.	Weak	Very low
IGRA for contact tracing in children	In children > 5 years, initiate contact tracing with TST, but in BCG-vaccinated contacts, positive TST results should be confirmed with an IGRA performed on the date of TST reading.	Weak	Very low
	In children < 5 years, test with TST and IGRA, regardless of previous BCG vaccination.		
IGRA in HIV-infected persons	Use both TST and an IGRA to detect TB infection in persons with HIV infection. In persons with HIV and a CD4 cell count <200/mL, use only an IGRA.	Weak	Low to very low
IGRAs in patients with chronic inflammatory diseases (prior to initiating biologic therapies)	Use both PT and an IGRA to screen for TB infection in patients with chronic inflammatory disease before starting biologic therapy.	Weak	Low to very low
IGRA for patients requiring transplantation (SOT and allogeneic HSCT)	Use both TST and an IGRA to screen for TB infection in patients who will undergo solid organ or allogeneic hematopoietic stem cell transplantation.	Weak	Very low
IGRA for active TB	Do not use either IGRAs nor TST as a stand-alone test for the diagnosis of active TB.	Strong	Low
	The panel suggests using an IGRA as a test for TB infection to support the diagnosis in cases with a well-founded suspicion of active disease.	Weak	Very low

TST: tuberculin skin test; BCG: bacillus Calmette-Guerin; IGRA: interferon gamma release assays; HIV: human immunodeficiency virus; SOT: solid organ transplantation; HSCT: hematopoietic stem cell transplantation.
Modified from reference [29]

sion such as pharmacologically induced ones increase the prevalence of TB and the shift towards greater presence of EPTB or disseminated forms. Corticosteroids and treatment with Tumor Necrosis Factor alpha (TNF alpha) inhibitors [42] are two good examples of this. In these patients, EPTB accounts for 62% of all TB episodes [43,44].

Another group at risk for EPTB are solid organ transplant recipients (SOT) where EPTB may account for up to 25% of the episodes of tuberculosis infection and where therapeutic problems increase due to the risks of interference with the immunosuppressive drugs that these patients receive [45,46].

Immunosenescence in the elderly may also be a factor in the drift towards a higher percentage of EPTB forms [47].

Large series of patients with TB followed prospectively in our setting are uncommon and therefore, we provide here information from a hospital in Madrid (Ruiz-Galiana J and Barros C, personal communication) that illustrate the reality of TB and EPTB in our environment. In this center, 1,820 patients with active tuberculosis have been systematically collected over the last 40 years (1983-2023), with a median age of 37 years; 6.5% under 14 years of age and 16% over 65 years of age. Overall, 22.7% were immigrants (mostly Africans) and 17% of all patients in the series were HIV-positive [48]. In this experience, 45% were EPTB (22.8% isolated EPTB; 17.7% disseminated and 5% with two non-contiguous organs). Tuberculous adenitis remains the most frequent location of EPTB with microbiological certainty and in fact should be a permanent consideration in the differential diagnosis in the presence of lymph node enlargement [49,50].

Osteo-articular TB, especially infection of the axial skeleton (Pott's disease), is still relevant [51] as does monoarticular arthritis (hip and knee preferentially). Central Nervous System (CNS) TB continues to cause mortality and sequelae and in these forms the role of adjunctive corticosteroid therapy may decrease both the one and the other [52,53].

Intestinal tuberculosis, at least in developed countries, has decreased significantly both because of the decrease of highly bacilliferous forms and because of the sanitation of the cattle population *(M. bovis)* [48,54]. In the aforementioned series, the incidence of genitourinary TB also shows a decrease [55].

WHAT IS THE STATUS OF MICROBIOLOGICAL DIAGNOSIS OF TUBERCULOSIS IN SPAIN?

The diagnosis of tuberculosis in Spain, as in other high-income countries, has undergone a profound transformation with the introduction of new technologies and methods in laboratories and Microbiology Departments. However, at present, conventional methods such as smear microscopy, staining of respiratory and urine samples to visualize and quantify the presence of *M. tuberculosis*, and solid media cultures for isolation and phenotypic susceptibility studies coexist with new diagnostic methods. The latter include liquid cultures with continuous growth monitoring and the simultaneous possibility of studying susceptibility to drugs active against *M. tuberculosis*, molecular biology techniques, essentially nucleic acid amplification by real-time PCR, and IGRAs, the latter complementing the classic TST [56,57]. The introduction of new techniques has been aimed at improving diagnostic sensitivity and reducing laboratory response times.

In 2017, the Ministry of Health published a document containing the results of a survey reflecting the situation of tuberculosis diagnosis in Spain and updating previous data published in 2009. These data were to serve to boost the Network of Tuberculosis Laboratories at the national level [58]. In the survey published in 2017, 154 laboratories from 18 Autonomous Communities participated. It reflected that almost half of the laboratories did not perform cultures as they sent them to other centers or only performed microscopy techniques. Almost 40% performed microscopy and culture techniques, identification of the *M. tuberculosis* complex and antibiograms for first-line drugs, and 13% also performed antibiograms for second-line drugs. Interestingly, almost 45% of the laboratories had already adopted among their techniques one or more molecular systems capable of detecting the *M. tuberculosis* complex and simultaneously detecting resistance to rifampicin and/or isoniazid with the possibility of applying them either on direct samples or once *M. tuberculosis* had been isolated in the cultures. Likewise, 13% of the laboratories reported performing genotyping of multidrug-resistant strains, with this type of study being sent to a reference center in 70% of the laboratories. Confirmation of outbreaks was only performed in a few laboratories.

This situation would have changed today with the incorporation as standard in the diagnosis of tuberculosis of liquid cultures and rapid techniques based on real-time PCR that simultaneously detect the presence of the complex and rifampicin resistance. More recently, similar molecular systems have been incorporated that broaden the study of resistance markers to include isoniazid, fluoroquinolones and also amikacin, kanamycin, capreomycin and ethionamide [59]. Also, the incorporation of whole genome sequencing systems in many laboratories in the wake of the COVID-19 pandemic could be used in outbreak characterization.

The still existing deficiencies in TB diagnostic technology in the world constitute an unsustainable anachronism [60].

WHAT IS MOLECULAR BIOLOGY CONTRIBUTING TO THE DIAGNOSIS AND MONITORING OF TUBERCULOSIS IN SPAIN?

The availability of rapid molecular assays for the identification of the *Mycobacterium tuberculosis* complex, and even for the characterization of resistance mutations against first- and second-line antituberculosis drugs, has optimized the diagnostic capacity of laboratories and the possibility of establishing appropriate treatments early. However, there has not been a parallel development in the incorporation of molecular approaches for the monitoring and control of transmission. The molecular characterization of transmission "clusters" has provided valuable information for the precise determination of population environments associated with active transmission, revealing contexts and transmission dynamics that lie outside the circles of exposure contemplated by conventional contact studies [61].

Despite the great advances made by molecular epidemiology, the great social complexity of our populations, as a result of the increase in the immigrant population, often associated with suboptimal living conditions after arrival in the receiving countries, has demanded the application of higher resolution techniques. The incorporation of whole genome sequencing has opened a new era of genomic epidemiology [62], which represents a further increase in the accuracy of defining TB transmission patterns.

New genomic strategies have allowed us to shed light on the complexity of TB transmission in populations with high migration rates. Thus, we have been able to understand that in addition to cases that can be accurately labelled as imported cases, which reactivate the disease in our country, we identify cases resulting from new exposures after arrival in our territory.

The high resolution provided by genomic analysis must be coupled to a new way of conducting epidemiological research. It is only in this way that the linkages pointed out by the identification of genomic clusters can reveal the transmission environments behind them. This new way of working involves reorienting the patient interview to contemplate the links suggested by the genomic study, for which the use of community health workers who facilitate access to detailed information on these migrant patients is essential. The application of these strategies in complex populations has made it possible to effectively manage transmission alarms and even to identify such unexpected realities as transmission throughout the migratory journey [63].

For this new genomic approach to provide epidemiologically relevant information, it is necessary to make a population-based analysis effort and to maintain systematic analysis over a prolonged period of time. Persistent outbreaks of great magnitude have been identified in populations in our country in which this approach was used [64]. This method helps to find strains responsible for a large percentage of the cases in a population as well as to understand with high resolution the

dynamics of transmission [65]. In addition, the globalization of the new epidemiological scenario requires the transnational expansion of molecular and genomic studies, integrating our data with those of circulating strains in the migrants' countries of origin and in other European countries that receive migrants of the same nationalities [66].

The new challenge is to ensure that genomic results are obtained more quickly, so that they can be offered early to those responsible for surveillance programs and to efficiently direct control resources towards the environments that are truly responsible for the generation of secondary cases. The emergence of alternative sequencing systems, faster and more flexible, and with a discrimination capacity equivalent to that of conventional sequencing systems [67] allows to maintain expectations of accessing a true approximation of genomic resolution at the time of diagnosis. Thus, with the same analytical effort, it would be possible to access not only the essential data for the characterization of whether a new case belongs to an active transmission chain or not, but also to extract complete information about resistance mutations [68] or determine whether the case corresponds to a species of the tuberculosis complex other than MTB. Recently, a major zoonosis caused by *Mycobacterium caprae* was indirectly revealed by the application of genomic sequencing for epidemiological purposes [69].

The systematic genomic analysis of SARS-CoV-2 performed during the pandemic in our country has led to the provision of equipment and training in genomic strategies. It would be unforgivable not to take advantage of these resources and experience to achieve a transformation in the way in which TB transmission is being monitored and to ensure a definitive leap in efficiency on our way to its control.

WHAT IS THE RESISTANCE TO ANTI-TUBERCULOSIS DRUGS IN EUROPE AND SPAIN?

The prognosis of TB patients was truly dismal until the advent of the so-called "chemotherapy era". About 50% of patients could die, half of them within the first 18 months of having the disease, and the other half within 5 years. Another 20-25% of patients remained chronically ill in the community, without being cured, but also without dying. And only about 25-30% of patients were cured, because the immune system never stopped fighting against this pathogen [70].

The so-called "TB chemotherapy era" can be considered to have started with the discovery of streptomycin (1943), followed by PAS (1944), isoniazid (1951), pyrazinamide (1952), ethambutol (1961), rifampicin (1963), etc. The discovery of these drugs was followed by the development of multiple randomized clinical trials involving them, either alone or in combination. All this occurred in the two decades from 1943 to 1963, years in which not only 11 drugs with different activity against *Mycobacterium tuberculosis* were discovered, but also the bases that should govern all TB treatment were laid [71-74].

However, following the development of the different anti-TB drugs, resistance of *M. tuberculosis* to each of them began to be described, all as a consequence of their misuse. *M. tuberculosis* once again showed its capacity to adapt to adverse environments, in this case developing resistance to the different drugs [74]. These resistances have become a major problem worldwide, making it difficult to control the disease. The most important are rifampicin-resistant TB (RR-TB), which is still the most effective drug for treating TB; and multidrug-resistant TB (MDR-TB, which refers to TB with resistance to isoniazid and rifampicin) [75]. When, in addition to RR-RR/MDR-TB, there is resistance to fluoroquinolones, it is called pre-XDR-TB (pre-extensively resistant TB). And XDR-TB (extensively resistant TB) which is pre-XDR TB, which also accumulates resistance to linezolid, bedaquiline, or both) [75]. The main problem of resistance is that in order to avoid its selection it is necessary to associate a minimum of 2-3 drugs in the treatment of TB, and currently there are only about 20, of which only eight can be considered highly effective [71,74].

Unfortunately, the misuse of anti-TB drugs in the 1970s to 1990s caused MDR/MDR-TB to reach epidemic proportions worldwide. And cases of what is now called pre-XDR-TB began to appear. And this epidemic situation has only increased over the years of the current century, influenced by multiple factors, starting with the aforementioned inadequate treatment regimens, poor adherence to such prolonged treatment, the transmission of resistant strains of *M. tuberculosis*, access to drugs, the quality of TB control programs, etc. [74]. In fact, of the estimated 10.6 million TB cases worldwide in 2021 (a figure 4.5% higher than in 2020), nearly half a million (450,000) were ill with MDR/XDR-TB. Of the 1.6 million people who died of TB in 2021, about 250,000 were also MDR/MDR-TB carriers [76]. Consequently, drug-resistant TB, especially MDR/MDR-TB, remains a serious global public health problem that has required significant investment in the development of new diagnostic methods and new drugs [74].

It is estimated that almost 50% of MDR/MDR-TB cases worldwide occur in China and India, and another 7% in Russia and former Soviet countries [76].

Globally, it has been estimated that the proportion of new cases of RR-TB/MDR-TB was 3.9% in 2015 and 3.6% in 2021. These percentages rose in patients previously treated for TB, being 20% in 2015 and 18% in 2021 [76].

The WHO estimated that in 2021 there could be around 210 cases of MDR/MDR-TB in Spain (ranges 70 to 340), implying a rate of 0.43 cases per 100,000 inhabitants (ranges 0.15 to 0.72) [76]. WHO also estimated that in that year about 4.4% of new TB cases were RR-TB/MDR-TB (ranges 2 to 8.2), rising to 20% (range 5.9 to 44%) in previously treated patients [76]. These figures are very similar to those estimated at the global level worldwide [76], although in Spain there seems to be a clear difference between the autochthonous population with low rates of MDR/MDR-TB and patients born outside our country, with clearly higher figures [77]. Unfortunately, there are hardly any publications addressing this issue

Table 3	Situations in which the administration of directly observed anti-tuberculosis drugs (DOT) is considered a priority.
Treatment failures	
Relapses	
Drug resistance	
Intermittent patterns	
Previous poor adherence	
Prior TB treatment or chemoprophylaxis	
Indigence	
Active or previous drug addiction (drugs, alcohol, ...)	
HIV infection	
Children and adolescents	
Mental disturbances, cognitive impairment, psychological disturbances	
Blindness, deafness and frailty	
Institutionalized patients	

in Spain, but the few that exist offer much lower data than those estimated by the WHO, estimating that MDR/MDR-TB would be around 1% of new TB cases [77,78,79], or around 40-60 cases per year.

Worldwide, isoniazid (hr-TB) has the highest rate of resistance, clearly related to its introduction into the world almost two decades ahead of rifampicin. Globally, it is estimated to be around 8-10%, with the Eastern European region reporting the highest rates of Hr-TB, reaching 33.5% in new cases and 61.4% in previously treated patients. [80]. Again, the limited data available for Spain suggest that this rate may be around 5% in new cases [76-79].

WHAT DO WE UNDERSTAND BY NEW ANTI-TUBERCULOSIS DRUGS AND WHAT DO THEY CONTRIBUTE TO TREATMENT? WHAT IS THEIR STATUS IN SPAIN?

As we have mentioned, the poor prognosis of TB changed radically in the two decades between 1943 and 1963, years in which 11 drugs with different activity against *M. tuberculosis* were discovered and proved to be very effective in different associations, with the capacity to cure almost all of these patients [71,72,74]. However, when a highly effective scheme was developed at the end of the 1960s, it was thought that this disease could be eliminated in the short term, and research into the development of drugs with activity against *M. tuberculosis* was discontinued. It took more than 40 years for bedaquiline to be investigated as a new specific drug against TB [81].

Among the more than 20 drugs that are currently available with activity against *M. tuberculosis* [74], the vast majority are still the classics that have been used for decades, of which there was only one very good (rifampicin) and one quite good (isoniazid), the others having moderate or very poor action in many of them [71,74,82]. But since there was a treatment regimen that worked very well in the field, there was no concern to develop new drugs. It was only when cases of TB with rifampicin resistance (RR-TB) and with resistance to rifampicin and isoniazid (MDR-TB) started to increase considerably and reached epidemic proportions that we started to talk about possible cases of incurable TB again [83]. This is what prompted countries with more resources to start researching new drugs for TB, and to test antibiotics that had been shown to be highly effective against other infections for this disease [74,76,84].

Thus, the category of so-called new anti-TB drugs includes those that have been specifically investigated for TB and those antibiotics that, although never investigated for TB, have been shown to be very effective against this disease. Of the former, of those specifically investigated for TB, bedaquiline, delamanid and pretomanid are already available on the market, the latter two having a very similar action as they are both nitroimidazole derivatives. All three have excellent bactericidal and sterilizing activity, as well as being very well tolerated and preventing the selection of resistance [71,74,85]. This makes them clearly better than several of the classic so-called first-line drugs, such as pyrazinamide and ethambutol, and although they are currently only recommended for the treatment of RR-TB/MDR-TB, in the very near future they will certainly be part of the initial treatment regimens for TB with anti-TB drug sensitivity. In addition, more than 15 drugs are currently being investigated for TB and are in clinical phases I, II, or III. This shows the interest that, fortunately, TB is once again attracting research interest in countries with more resources.

On the other hand, there are other drugs that, although investigated for other infections, have been shown to be highly effective for TB. Among them are the fluoroquinolones moxifloxacin and levofloxacin, linezolid and clofazimine. All of them also have excellent bactericidal (except clofazimine) and sterilizing activity, as well as being well tolerated and preventing the selection of resistance [71,74,85]. This also means that in the very near future they will be part of the initial treatment regimens for TB. Finally, we can also consider as new drugs those that belong to families of so-called first-line drugs, but with some additional characteristics that can make them more effective in specific circumstances. This is the case of the rifamycins, rifabutin and rifapentine, which are quite similar in their action to the other rifamycin, rifampicin, but with a lower enzymatic induction in the microsomal cytochrome P450 in the former and a longer half-life in the latter. This is why rifabutin can be a very valid option in cases where the enzymatic induction of rifampicin can be a problem for the treatment of other diseases in which its drugs are metabolized in this cytochrome, as can happen with some anti-retroviral drugs and many other drugs [86]. And the longer half-life of rifapentine means that it can be used in weekly preventive treatment schemes (12 weekly doses of isoniazid plus rifapentine) [87], o that, with daily administration, their concentrations can be progressively increased and thus increase their sterilizing action, making it possible to shorten preventive treatment schedules (1 month with isoniazid plus rifapentine) [87] and curative of TB [88].

Therefore, the discovery of the so-called new drugs for the treatment of TB has been a major breakthrough in the treatment of this disease, especially because almost all of them are more effective than most of the previous ones (except rifampicin) and all of them have a very good sterilizing activity, which means to be able to shorten the treatment of tuberculosis infection and TB with drug sensitivity and resistance [71,74,85].

Unfortunately, access to some of these new drugs in Spain is quite difficult, in addition to being extremely expensive, as is the case with bedaquiline, delamanid and pretomanid, drugs that should now be considered in the first line of treatment of MDR/MDR-TB [71,74,75,85]. But one must be insistent in obtaining them, as they improve the prognosis with respect to the drugs previously used in the treatment of these forms of the disease. It can also be somewhat complicated to obtain clofazimine, although much less so than the previous ones. Fortunately, in Spain there is no problem in obtaining the fluoroquinolones levofloxacin and moxifloxacin, nor linezolid. Finally, however, it is still impossible to obtain rifapentine, since the European and Spanish Medicines Agencies have not yet approved it for use in Europe and Spain [89]. It is desirable that this situation will change in the very short term since, as has been mentioned, this drug is now part of shortened TB preventive and curative treatment schemes.

WHAT IS THE REALITY OF DIRECTLY OBSERVED (DOT) TREATMENT IN SPAIN?

Once the tuberculosis disease has been diagnosed and the appropriate treatment regimen has been selected, most patients should be cured, if they follow the treatment correctly. In high-income countries, most patients receive self-administered treatment. However, WHO data estimate that between 50-80% of patients on self-administered therapy do not take their treatment properly, especially 6-8 weeks after the start of treatment [90]. Poor adherence conditions the appearance of failures, relapses and/or selection of resistance. For decades, the WHO has been recommending supervised or directly observed therapy (DOT), which consists of seeing and ensuring that the patient takes the medication, ideally in the presence of healthcare personnel, rather than by members of the patient's entourage. With DOT, the probability of treatment completion increases to almost 90% [91]. DOT is also endorsed by other institutions including the American Thoracic Society (ATS), the Center for Disease Control (CDC) and the Infectious Diseases Society of America (IDSA) [3].

New technologies (SMS, cell phone alarms, video calls, etc) allow the use of systems that are less expensive than face-to-face DOT, but are not applicable to many patients. As of March 2023, CDC includes video (vDOT) as an alternative to face-to-face DOT [92].

In Spain, the implementation of DOT is very slow and is usually restricted to patients with a higher risk of poor adherence (Table 3). In addition to supervising the taking of pills, other actions such as: the provision of food, transport vouchers, psychological support, social workers, reminders or accompaniment for complementary tests and consultation check-ups, etc. help to achieve the objective. Although the ideal is to supervise daily intake at home, the DOT team could adapt, depending on the characteristics of the patients and the type of TB, to follow less strict guidelines (no weekends or holidays, allowing some short trips, etc.).

In Madrid, there is a DOT program that has been carried out by the Red Cross since 2002, which can be accessed by any hospital or primary care physician. Trained professionals (nurses and assistants) are distributed by health areas and go to the patient's home or to a previously agreed place to provide them with oral medication and even IM drugs (Streptomycin, Amikacin) if necessary. This structure and organization has been used for other medical needs such as detection of risk contacts, chemoprophylaxis in the family environment and even supervision of patients with problems unrelated to TB such as pregnant women with HIV infection requiring antiretroviral treatment, chronic hepatitis due to HCV or patients with atypical mycobacteria who, "a priori", are suspected to be poor compliers.

In the University Hospital of Móstoles over the last 20 years, the Red Cross DOT program has been used progressively (Barros C and Ruiz-Galiana J, unpublished data), reaching 409 episodes (65.4%) of the 625 diagnosed in this period of time with excellent results (only 3 failures, including 2 exitus). In recent years, more than 90% of the patients in this cohort, diagnosed with TB disease, joined the DOT program. The current question in such a situation is the selection of patients who do not require DOT and who can do the complete treatment on their own, without supervision. In some patients, where home treatment is not possible, DOT can be performed in long-stay centers (former "tuberculosis sanatoriums", old people's homes, psychiatric hospitals, prisons, etc..) or on an outpatient basis in drug dependency centers (DAC), soup kitchens or shelters.

HOW LONG AND HOW CAN THE DURATION OF ANTI-TB TREATMENT BE SHORTENED?

Difficulties in adherence to and completion of classic antituberculosis treatment led to the search for shorter duration regimens that would facilitate better compliance, allowing treatment to be completed more quickly. This search has been carried out both in patients with tuberculosis caused by microorganisms sensitive to anti-tuberculous drugs and in those caused by MDR or XDR mycobacteria.

Some of these regimens are outlined below:

Short regimens in drug sensitive tuberculosis

Regimen of choice: R (Rifampicin) I (Isoniazid) P (Pyrazinamide) E (Ethambutol) RIPE 2 months + IR 4 months

As opposed to the classic 9-month RIPE treatment, the current regimen of choice for tuberculosis in which resistance to first-line drugs is known or suspected to be absent is the

combination of RIPE, administered during an intensive phase of 2 months, followed by a consolidation phase of IR, administered for a further 4 months [93]. If it is confirmed that there is no resistance to isoniazid, ethambutol can be withdrawn from the intensive phase for the same duration. Only in case of cavitary disease and with persistent positive cultures at the end of the intensive phase is it recommended to extend the consolidation phase for an additional three months.

Alternative 1: RIPE 2 months + RI 2 months

Pulmonary tuberculosis can often be diagnosed in patients with compatible clinical and radiological findings in whom microbiological studies (stains, cultures) are negative. In these circumstances, in which it is assumed that the bacillary load should be low, the results of shortening conventional treatment have been investigated. Several studies have shown that reducing the time of RIPE administration from 6 to 4 months did not influence the rate of tuberculosis relapse [94-96]. For this reason, the most recent guidelines recommend that, after the initial phase of treatment with RIPE, the consolidation phase with isoniazid and rifampicin can be shortened to only two months [93]. This short regimen could be administered to HIV-negative individuals with culture-negative pulmonary tuberculosis in whom the clinical and radiological evolution is favourable after the two-month intensive phase. Treatment should not be shortened if there are doubts about the adequacy of the microbiological evaluation or if the response in the initial two months has not been good.

Alternative 2: Rifapentine-moxifloxacin 4 months

The efficacy of a 4-month regimen including rifapentine and moxifloxacin was recently reported [97]. This regimen for sensitive tuberculosis consists of an 8-week intensive phase of daily treatment with rifapentine, isoniazid, pyrazinamide, and moxifloxacin, followed by a 9-week continuation phase of rifapentine, isoniazid, and moxifloxacin (total of 17 weeks). According to the CDC, this short regimen would be an option for persons with TB lung disease caused by bacteria in whom drug resistance is not suspected, who are older than 12 years and weigh more than 40 kg, have a negative sputum culture (low mycobacterial load), and are not receiving medications that may interact with drugs in the regimen. In the case of persons with HIV, the CD4 count should be greater than 100 cells/microliter [98].

Short regimens in resistant tuberculosis

According to WHO and ATS/CDC/ERS/IDSA recommendations, patients with resistant tuberculosis should receive a long course of treatment with a total duration of 18-20 months or 15-17 months after culture conversion, with the possibility of modifying the duration depending on response [99]. In this long treatment, drugs are individualized and administered during an intensive phase extending 6 months after sputum culture conversion (performed two months after initiation of management). Subsequently, a continuation phase of 15-17 months from the time of sputum culture conversion is administered, continuing all drugs from the intensive phase except for bedaquiline, amikacin and streptomycin. In contrast to this long treatment, a short regimen that is standardized is proposed. Its efficacy was derived from a meta-analysis of observational studies [100] and was later confirmed in the STREAM study, a randomized clinical trial [101]. It starts with a 4-month intensive phase of moxifloxacin, kanamycin (or amikacin), prothionamide, clofazimine, high-dose isoniazid (15-20mg/kg/day), pyrazinamide and ethambutol which is extended to 6 months for smear positive and culture positive patients 2 months after initiation of treatment. Subsequently, a 5-month continuation phase of ethambutol, pyrazinamide, moxifloxacin and clofazimine is administered for a total of 9 to 11 months. The short regimen can be considered in patients who have not received previous treatment for more than 1 month with second-line drugs and in whom resistance to fluoroquinolones and injectable second-line drugs is excluded. Pregnant women, persons with extrapulmonary tuberculosis in coinfection with HIV or disseminated TB, meningeal or in the central nervous system are also excluded. In these circumstances, the long regimen should be administered. It should be noted that, although the short regimen has been recommended by the WHO, it has not been supported in the most recent recommendations of the ATS/CDC/ERS/IDSA, which consider that it has drawbacks, the evidence is inconclusive and call for the need to generate more evidence [93].

WHAT IS THE RISK OF RELAPSE FOR A PATIENT WITH WELL-TREATED TUBERCULOSIS?

According to WHO, recurrences of tuberculosis account for approximately 7% of incident cases [102]. A meta-analysis of [103] data from 145 countries suggests that the incidence of recurrent TB is 2.26 per 100 person-years, with a wide range between 0.05 and 29.52. This variability reflects the different definitions of recurrence and the settings in which it is analyzed, which include the comorbidities of the population, its socioeconomic level and bacteriological aspects, among others [104]. This is an issue of great importance in TB management programs, because recurrence is most often associated with resistance to treatment [102], and people with recurrent infection have a worse prognosis [102].

The most common cause of recurrence is lack of full adherence to treatment and it has been observed that administration under direct control can reduce recurrence rates by approximately 75%. However, the possibility of recurrence still exists [105].

Recurrences may be due to reactivation of the original strain (reactivations) or infection with a new strain (reinfections) [106]. The ratio of one to the other in recurrent episodes depends on several factors, including the adequacy of treatment and exposure to environments with high incidence of TB [103,107,108].

With respect to host characteristics, male sex, advanced age, low weight, smoking, diabetes or HIV infection are associated with a higher risk of recurrence [109-111]. From the social point of view, low income, low social or cultural level, immi-

grant status and prison stay are also factors associated with the risk of recurrence [107,109]. With respect to the first infection, the existence of cavitations and the persistence of *M tuberculosis* in the sputum two months after initiating treatment predict recurrence, most likely due to reactivation [107,109].

Most recurrences occur within the first two years of the first episode [110, 112], almost all of them (85%) in the first one [110], It therefore seems necessary to have a minimum follow-up period of one year after completing treatment, in order to diagnose them early. From the point of view of individual prevention, it seems necessary to insist on the need to correctly complete treatment, ensure the nutritional and health status of patients and help them to quit smoking. It is possible that pharmacological secondary prevention of TB may be useful in HIV patients [113], although prospective randomized studies are not available.

WHAT PROBLEMS DOES TUBERCULOSIS POSE AT PRESENT IN THE SURGICAL WORLD?

At present, the role of surgery in the treatment of tuberculosis has been relegated to treat its complications in those with poor clinical response or intolerance to medical treatment.

Surgery is considered when sputum cultures remain positive after four to six months of antituberculosis treatment and in the presence of complications (massive hemoptysis, persistent bronchopleural fistula, residual cavities, bronchial stenosis, pachypleuritis, tuberculous empyema) [114,115].

Surgery for tuberculosis is complex, due to the existence of numerous adhesions, pachypleuritis, pleural contamination and the presence of contaminated caverns in the parenchyma. Measures must be taken to avoid contamination of the contralateral lung, such as using a double-lumen tube for intubation. In general, surgery should be performed only after several months of antituberculous therapy, after negative cultures (if possible) [114,115].

Surgical techniques are diverse and are conditioned to the pulmonary functional reserve. These techniques cover a wide spectrum, from anatomical resections to temporary thoracostomies. In a meta-analysis [116] involving more than 6,000 patients, partial lung resection surgery was associated with greater treatment success (defined as no treatment failure and no relapse), but pneumonectomy was not. Treatment success was more likely when surgery was performed after culture conversion than before.

IS TUBERCULOSIS A CONCERN IN INTENSIVE CARE UNITS?

Approximately 3% of TB patients require admission to Intensive Care Units (ICU) with a high mortality rate (between 24 and 81%) depending on the social and geographical context [117].

The most frequent indication for admission to the ICU for TBI is acute respiratory failure due to pneumonia or acute respiratory distress syndrome (ARDS), which may or may not be accompanied by miliary tuberculosis, followed by septic shock with multiorgan dysfunction, adrenal insufficiency, tuberculous meningitis, and pericarditis. Other causes include thromboembolic disease, pulmonary haemorrhage, or pharmacological complications [118].

ARDS is the most frequent cause of admission to the ICU, although only 4% to 5% of ARDS are secondary to tuberculosis. Mortality in patients with ARDS reaches 60% in those requiring mechanical ventilation [119]. The nonspecific clinical and radiological findings require a high index of suspicion to reach a diagnosis. The management of ARDS is similar to that of other etiologies, being necessary to maximize protective ventilation measures, prone decubitus, sedation and deep relaxation. Recruitment manoeuvres should be performed with caution due to the high risk of pneumothorax.

Tuberculous meningitis is the second leading cause of admission to the ICU in tuberculosis patients, representing between 6% and 18% of all ICU admissions for TB. It is especially frequent in children, patients with miliary or disseminated TB and HIV coinfection. The most severe patients require neurocritical monitoring. Corticosteroids are used in conjunction with anti-TB drugs to reduce cerebral edema and reduce short-term mortality [120].

Despite adequate treatment, tuberculous meningitis has a high mortality (60%) and morbidity with residual neurological disability in 25% of cases.

Septic shock is generally associated with bacterial or other respiratory super-infection, with tuberculosis accounting for only 1% of the cases of septic shock in the ICU. It is very infrequent in immunocompetent patients and is associated with a very high mortality (80%) compared to other types of shock (48%). In patients with high clinical suspicion of TB, early initiation of empirical antituberculosis treatment is recommended, being the management of shock similar to that of other causes (fluid therapy and use of vasopressors). In refractory shock, adrenal insufficiency should be suspected and the administration of hydrocortisone (200-300 mg) should be considered [121].

Adrenal insufficiency is observed in 6 to 10% of patients with active TB due to direct involvement of the adrenal glands, hematogenous spread or the use of drugs such as rifampicin which increases cortisol metabolism and can cause functional adrenal insufficiency. In these cases the determination of plasma cortisol levels and the administration of hydrocortisone at doses of 300-400 mg /24 h or prednisone is recommended, avoiding dexamethasone because of its cushingoid side effects. Fludrocortisone should be added in patients with associated aldosterone deficiency.

The diagnosis and treatment of TB in critically ill patients poses several challenges, such as adequate specimen collection. Sputum or induced sputum is recommended in patients with noninvasive ventilation and endotracheal aspirate or bronchoalveolar lavage in patients with invasive mechanical ventilation. Appropriate samples should be taken from other locations according to the clinic such as pleural fluid, ascitic fluid and CSF or fine needle aspiration of peripheral lymph nodes.

In patients with high clinical suspicion, specific empirical treatment is essential. The characteristics of the critically ill patient, the route of administration, drug absorption, bioavailability, dose modification in case of hepatic and renal dysfunction, and interaction with other drugs should be considered to ensure adequate plasma levels. Conventional regimens (rifampicin, isoniazid, pyrazinamide and oral ethambutol) have been shown to reduce mortality compared to alternative regimens (IV levofloxacin plus oral ethambutol plus IM streptomycin or IV amikacin, without rifampicin or isoniazid) [122]. Suboptimal concentrations of some drugs lead to recommend the intravenous use of specific treatments that are not always available in all countries. The presence of MDR-TB should be considered if the patient comes from high-risk regions, has been previously treated with first-line drugs or has failed to respond to standard treatment [123].

Some patients present a paradoxical reaction after initiation of antituberculosis drugs characterized by rapid clinical deterioration (worsening or appearance of new lesions, airway obstruction, splenic rupture or neurological deterioration) due to reconstitution of immunity leading to an immune response against the bacilli. Corticosteroids are the mainstay of treatment.

Factors associated with high mortality in critically ill patients have been associated with age, presence of multiorgan dysfunction syndrome, sepsis, need for mechanical ventilation, development of nosocomial pneumonia, cardiogenic shock, renal failure, elevated APACHE II, HIV infection, low albumin, and delayed or inadequate treatment, among others [124]

Finally, it is necessary to isolate these patients, ideally in negative pressure rooms, reduce the procedures that generate the formation of droplets and aerosols, use closed suction systems and filters (in the expiratory branch) in mechanically ventilated patients and the use of personal protection measures including FP2 and FP3 masks by professionals according to the procedures.

WHAT IS NEW IN THE DIAGNOSIS AND TREATMENT OF CHILDHOOD TUBERCULOSIS?

Pediatric TB remains a major global health problem, with 1,200,000 new cases and 216,570 deaths by 2021, accounting for 12% of the global burden of the disease [102]. The risk of progression from infection to disease is substantially higher in children than in adults: approximately 30%-40% of infants and 10%-20% of children with latent infection progress to disease within 2 years of primary infection [125].

Definitive diagnosis of TB in children is difficult to establish due to the lack of specific signs and symptoms, difficulties in obtaining sputum samples, and the paucibacillary nature of the disease in this age group. As a consequence, less than half of children with TB have microbiological confirmation, despite improvements in diagnostic tools in recent years.

The cornerstone of the diagnosis of TB in children continues to be the chest X-ray (CXR), in postero-anterior and lateral projection [126], despite its low specificity and poor inter-observer agreement [127]. Computed tomography (CT) is more sensitive than CXR, but its systematic performance is not indicated due to the emission of ionizing radiation and the need for sedation in younger children [128]. Indications are [129]:

1) asymptomatic children with known contact, positive TST/IGRA and inconclusive CXR (or normal in <2 years),

2) symptomatic children with known contact, positive TST/IGRA and normal CXR, 3) immunosuppressed children with known contact, normal CXR, regardless of TST and/or IGRA,

4) children with doubtful or pathological CXR with possible airway compression or other complications that require further definition of the affected structures [129].

It can be very useful for the evaluation of recently infected children with lesions not evident on chest X-ray, as in the study of school outbreaks [7]. Thoracic and mediastinal ultrasound are increasingly used at the bedside to visualize consolidations, cavitations and miliary nodules [130] whenever they are in contact with the pleura, as well as mediastinal and, with more difficulty, hilar lymphadenopathies [131].

The sensitivity of immunodiagnostic techniques for TB infection in children, such as the TST and IGRAs, is lower than in adults. Recent studies show that the performance of the latest generation of IGRAs, QFT-Plus, is no better than the previous generation, QTF-Gold, or the TST: neither of these tests has sufficient sensitivity as a rule-out test in children with suspected TB disease [132]. Individually, their sensitivity is around 70-80%, but in combination it exceeds 90 [133]. For this reason, the recent Spanish pediatric guidelines [129] recommend performing both techniques to screen for infection in high-risk patients (immunocompromised patients of any age and under 2 years of age, extendable to 5 years in high-risk exposures), and performing only one, TST or IGRA, to screen for infection in low-risk patients (over 5 years of age, not immunocompromised). In patients with clinical suspicion of TB, both techniques are recommended in combination to maximize diagnostic possibilities (Tables 1 and 2).

As for microbiological diagnosis, smear microscopy and culture have suboptimal sensitivity in children (<15% and <50%, respectively) [134]. New molecular techniques such as GeneXpert have good sensitivity with respect to culture (66-81%) [135,136], offering rapid diagnosis in smear-negative children, they are recommended by the WHO for the diagnosis of pulmonary TB [126]. In recent years, several studies have demonstrated the usefulness of molecular diagnosis in stool samples, also endorsed by the WHO in the most recent guidelines, which is promising as it is a non-invasive sample [126,137]

Regarding new therapeutic developments [129], The doses of antituberculous drugs in children are shown in Table 4. The administration of treatment in this age group is particularly difficult since, with the exception of rifampicin syrup, they are not available in liquid formulations. Fixed-dose combination drugs ("FDCs") base their posology on the adult dose range, and are only authorized for use above a certain age and/or weight.

Table 4 Recommended doses of first-line antituberculosis drugs [129]

Drug	Dose in mg/kg/day (dosage range); maximum daily dose (in mg)	Comments
Isoniazid*	10 (7-15); 300	Risk of hepatotoxicity
Rifampicin	15 (10-20); 600	Poor CNS penetration; risk of hepatotoxicity
Pyrazinamide	35 (30-40); 2000	Risk of hepatotoxicity, skin toxicity or arthralgias
Ethambutol	20 (15-25); 2500	Poor CNS penetration; risk of optic neuritis

*** Pyridoxine (1-2 mg/kg/day; maximum 50 mg/day) should be supplemented if exclusive breastfeeding, vegetarian diet, malnutrition, patients with HIV infection and pregnant adolescents.**

A recent document provides practical recommendations for the administration of TB treatment in this age group [138].

Prophylaxis in contacts. Children under 5 years of age and immunosuppressed children in contact with a case of bacilliferous TB, once TB disease has been ruled out, should receive post-exposure prophylaxis with Isoniazid during the window period (8-12 weeks) until the immunodiagnostic study is repeated. Children older than 5 years who are not immunosuppressed do not require post-exposure prophylaxis during the window period.

Treatment of latent infection. Children with positive TST/IGRA, asymptomatic, and with normal imaging test, should receive treatment of latent infection. As a first choice, short regimens are recommended, such as H+R for 3 months [139], or R in monotherapy 4 months [140], better than the long regimens of H 6 months or H 9 months. Efficacy is similar in all regimens, with better compliance and lower toxicity in the short regimens.

Treatment of TB disease. In children with uncomplicated TB disease, the short 4-month regimen is recommended, based on the recently published SHINE trial [141], consisting of HRZ ± E for 2 months, followed by H+R for 2 months, provided the following criteria are met:

- Age between 3 months and 16 years.
- Negative smear microscopy.
- Non-severe disease: peripheral adenitis; intrapulmonary adenitis without airway obstruction; non-cavitated lung disease, limited to one lung lobe without miliary pattern, with/without uncomplicated pleural effusion.
- Strain susceptible or presumably susceptible to first-line drugs (H, R, Z and E).

In all other cases, conventional 6-month treatment should be administered, consisting of HRZ ± E for 2 months, followed by H + R for 4 months.

Treatment should be prolonged in children with osteoarticular TB (9-12 months), disseminated and miliary TB (6-12 months) and TB meningitis (at least 12 months). In children with TB of the central nervous system, intensive treatment with HRZ and ethionamide (ethionamide 15-20 mg/kg/day, maximum 1000 mg/day; 250 mg tablets) for 6 months could be considered, due to the better bioavailability of ethionamide in CSF compared to ethambutol. This regimen, implemented in high-burden countries, is not recommended in HIV-infected children.

WHAT IS THE CURRENT STATUS OF TUBERCULOSIS VACCINES?

There is currently only one licensed vaccine against tuberculosis, BCG (Bacille Calmette-Guérin). BCG, with more than a century of use and with variable protection against respiratory transmissible forms of the disease, is historically the most widely administered vaccine worldwide. It is estimated that about 4 billion doses of BCG have been administered, mainly in the context of routine immunization of newborns.

BCG is administered intradermally and at birth and its vaccination is recommended by the WHO and is included in the vaccination schedule of countries with a high incidence of tuberculosis. It is estimated that BCG vaccination coverage is close to 90% worldwide [142,143]. Based on WHO recommendations, BCG vaccination is not indicated in countries with a low incidence rate of the disease, defined as less than 10 cases of TB per 100,000 population per year.

BCG is a live attenuated vaccine derived from a strain of *M. bovis* belonging to the *Mycobacterium tuberculosis* complex that causes bovine tuberculosis. BCG was developed in 1921 by attenuation through successive passages of a strain isolated from a cow. This isolate was subsequently distributed to several laboratories around the world and after repeated subculture passages several different BCG vaccine strains were developed with multiple changes in the genome [144]. The main reason for BCG attenuation is the loss of the differential region 1 (RD1). In this RD1 region is located the gene coding for the ESAT-6 protein, which when secreted is one of the major virulence factors of the *M. tuberculosis* complex. ESAT-6, together with two other proteins encoded in this RD1 deletion, CFP10 and PPE 68, are potent antigens that are conserved in clinical isolates of *M. tuberculosis* and their loss in BCG, in addition to causing its attenuation, may be one of the causes of the lack of protection of BCG against pulmonary tuberculosis. The ESAT-6 and CFP-10 antigens are used in Interferon Gamma Release Assays (IGRAs) to differentiate BCG vaccination from *M. tuberculosis* infection.

In 1921, the first baby whose mother had died of TB after birth was vaccinated with BCG orally. In the following 6 years, more than 50,000 infants were vaccinated, demonstrating that the live attenuated BCG vaccine was safe and could protect against other infectious diseases. This "non-specific" effect of live attenuated vaccines would be at the origin of the significant decrease in all-cause mortality in "vaccinated" (less than 2 %) compared to mortality in "unvaccinated" (25 %). BCG, like other live attenuated vaccines, confers non-specific indirect beneficial effects through generalized stimulation of the immune system, which can protect against other pathogens. Since the 1960s, BCG has demonstrated its value as an immunomodulator, specifically in the chemotherapy of bladder cancers. The non-specific effects of BCG and other live attenuated vaccines were described by Peter Aabey and this mechanism of action is currently being studied in depth by Mihai Netea's team [145]. BCG administration at birth is able to induce a strong Th1-type immune response and has been shown to decrease the number of hospitalizations due to respiratory infections and sepsis [146].

BCG offers protection with 60-80% efficacy against meningeal and miliary TB, disseminated forms of tuberculosis that are accompanied by high mortality and occur mainly in childhood [147]. However, protection against pulmonary TB, the transmissible form of the disease, is variable, especially in adolescents and adults [144].

Since the 1990s, the association of HIV/AIDS and TB and the emergence of resistant strains have made it a priority to develop a new vaccine to protect against respiratory forms. As of 2023, 16 new vaccines are in various stages of clinical development, with the aim of protecting against respiratory forms of the disease and reducing its transmission.

Five of these vaccine candidates, or vaccine strategies, are in Phase 3 to study their efficacy. Among these candidates are the GamTBvac vaccine candidate, based on two protein subunits containing the ESAT-6 and CFP-10n antigens or the inactivated whole cell candidate MIP, based on *Mycobacterium indicus* pranii not belonging to the *M. tuberculosis* complex. Three other approaches use live attenuated vaccines among them the revaccination strategy with current BCG in adolescents and adults previously vaccinated with BCG at birth, secondly the vaccine candidate VPM1002, based on the use of recombinant BCG encoding for *Listeria* hemolysin and efficacy studies look for non-inferiority to current BCG and thirdly MTBVAC, the only candidate based on a live attenuated strain of a human isolate of *M. tuberculosis*. With respect to MTBVAC the main advantage over the other candidates is that it contains a larger repertoire of *M. tuberculosis* antigens. MTBVAC contains the genes encoding the immunodominant antigens absent in BCG, without causing virulence and safely provides more specific and durable immune responses in humans than BCG. Ongoing double-blind efficacy studies of MTBVAC are looking for greater protection than BCG against TB, with MTBVAC being a promising candidate [148].

If Phase 3 efficacy studies of any of these candidates show protection against TB disease superior to that obtained with BCG, a new generation of TB vaccines could be licensed in the next few years. Improved diagnosis, shorter duration treatment of TB, and the potential availability of a new vaccine effective against respiratory forms of the disease could make the dream of eradicating TB possible.

WHAT OBLIGATIONS AND LEGAL IMPLICATIONS ARE ASSOCIATED WITH THE CONFIRMATION OF A CASE OF ACTIVE TUBERCULOSIS IN SPAIN, AND WHAT ETHICAL ASPECTS SHOULD BE HIGHLIGHTED IN THIS REGARD?

Law 33/2011, General Law on Public Health in Spain, establishes the bases for the protection of health and the prevention of communicable diseases. According to this law, health authorities have the power to implement measures to control and prevent the spread of communicable diseases. If a person is diagnosed with TB, the health authorities must take measures to ensure that he/she receives appropriate treatment. These measures include notifying the competent authorities of the case, recommending or requesting treatment, monitoring compliance with treatment and, in exceptional situations, taking coercive measures to ensure treatment, such as compulsory hospitalization. When patients are offered TB treatment, they should usually be informed and their verbal consent should be sought [149]. It is important to emphasize that the goal is to show respect for the patient and thus increase the likelihood of treatment completion. Patients who refuse treatment or are noncompliant should be counselled about the risks to themselves and the community. Similarly, the physician should try to understand the reasons for the patient's refusal or noncompliance with treatment and attempt to select a method to overcome these difficulties. If the situation of refusal or noncompliance persists, the patient should be informed that, although he/she has the right to refuse care, if he/she has active tuberculosis and does not complete the required course of treatment, he/she may be placed in isolation or involuntary detention.

In this regard, several management options should be considered:

- Community management: In cases where patients are willing to receive treatment, isolation and detention are generally not necessary or appropriate. Home treatment of tuberculosis patients, with the adoption of appropriate infection control measures, does not generally expose other household members to any substantial risk. By the time a diagnosis is made, household contacts have already been exposed to the patient's infection, and the likelihood of contact infection decreases rapidly when treatment is initiated. Even in cases of patients who have MDR-TB or XDR-TB, community-based treatment models have been successfully implemented in a variety of settings [150-152].

- Isolation or detention should be limited to exceptional circumstances when the patient is:
  - contagious, and refuses treatment and all reasonable measures to achieve compliance have been attempted with unsuccessful outcome.
  - infectious and refuses to undergo evaluation, follow-up for infection.
  - contagious, has accepted outpatient treatment but does not have the capacity to establish adequate infection control.

It is necessary to clarify that in no case can treatment be imposed on patients who have TB despite their opposition. These patients should be given the opportunity to receive treatment, but if they do not accept it, their informed refusal should be respected, since, once isolated, the patient does not represent a risk to public health. Forcing these patients to receive treatment against their will is neither ethically nor legally admissible according to the principle and law of personal autonomy.

Isolation or detention should be considered exceptional, only when it is the only reasonable means of protecting the population. It should always follow the ethical and legal principles of:

- Be applied in accordance with the law based on a legitimate objective.
- Be the least intrusive and restrictive possible.
- Not be arbitrary, unreasonable, or discriminatory.

These principles are not legal obligations, they are a reflection of fundamental ethical values [149] such as the common good, patient participation and autonomy in decision making, effectiveness of the use of measures with plausible outcomes, and transparency and accountability in that measures are adopted in a manner open to all, with a fair, sensitive and evidence-based decision-making process.

In Spain, there is experience of actions by public health services to prevent the transmission of TB by non-compliant bacilliferous patients using the possibilities of Law 3/1986 (which is the Organic Law 3/1986, of April 14, 1986, on Special Measures in Public Health) [153]. They are based on the health authority's resolution of the need for localization and compulsory therapeutic hospitalization to administer the treatment, mobilizing police collaboration, communicating it to the affected person and requesting ratification by the Administrative Court. From July 2006 to June 2015, over 9 years, in this experience, such measures were only activated on 12 occasions. The authors conclude that such coercive legal measures should be used with prudence and proportionality, with the aim of allowing patients at high risk to be treated in their environment, thus reducing community transmission of infection [3].

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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