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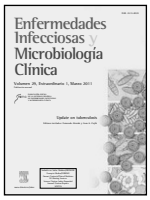

# Present epidemiology of tuberculosis. Prevention and control programs

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A B S T R A C T

Tuberculosis (TB) has affected humanity since the beginning of the recorded time and is associated with poverty, malnutrition, overcrowding, and immunosuppression. Since Koch discovered the infectious nature of the disease in 1882, knowledge about its history and physiopathology has advanced, but it continues to be a global public health problem.

More than 9 million new cases occurred in 2008 worldwide (with an incidence of 139/100,000 inhabitants), of whom more than one million died. Over half million of the cases presented with multidrug resistant-TB. Africa represents the continent with the highest incidence and the most HIV co-infection. The situation in Eastern Europe is also worrisome because of the high incidence and frequency drug resistance.

In developed countries, TB has been localized in more vulnerable populations, such as immigrants and persons with social contention. There is an increase of extra-pulmonary presentation in this context, related to non-European ethnicity, HIV infection, and younger age. In Spain, the increasing immigrant population has presented a need to improve coordination between territories and strengthen surveillance.

The global control plan is based on the DOTS strategy, although the objectives and activities were redefined in 2006 to incorporate the measurement of global development, and community and healthcare strengthening. Adequate control measures in a more local context and continual activity evaluation are necessary to decrease the burden of suffering and economic loss that causes this ancient disease.



## Epidemiología actual de la tuberculosis. Programas de prevención y control

*Palabras clave:*
Tuberculosis
Vigilancia
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Inmigración

R E S U M E N

La tuberculosis (TB) afecta a la humanidad desde tiempos inmemoriales y se asocia a la pobreza, mala alimentación, hacinamiento e inmunodepresión. Desde que Koch descubrió su naturaleza infecciosa en 1882, se ha avanzado mucho en el conocimiento de la historia natural y la fisiopatología de la infección, pero, sin embargo, continúa siendo un problema global de salud pública.

En 2008 ocurrieron más de 9 millones de nuevos casos en el mundo (incidencia de 139/100.000 habitantes) de los que más de 1 millón falleció. También más de medio millón de casos presentaron TB multirresistente. África es el continente con mayor incidencia y el más afectado por la coinfección por el virus de la inmunodeficiencia humana (VIH). Es preocupante la situación epidemiológica del este de Europa por su elevada incidencia y resistencia a los fármacos.

En los países desarrollados, la enfermedad se está concentrando en poblaciones vulnerables, como inmigrantes y personas con exclusión social. En este contexto aumentan las localizaciones extrapulmonares, relacionadas con etnias no europeas, infección por VIH y menor edad. En España, el aumento de la proporción de inmigrantes pone de manifiesto la necesidad de mejorar la coordinación territorial y fortalecer la vigilancia.

La estrategia global de control se ha basado en la estrategia DOTS, aunque en 2006 se redefinieron los objetivos y actividades incorporando medidas globales de desarrollo y fortalecimiento de las comunidades y de los sistemas sanitarios. La adecuación de las medidas de control al contexto específico y la evaluación continuada de las actividades son imprescindibles para conseguir disminuir la carga de sufrimiento y las pérdidas económicas que causa esta vieja enfermedad.



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## Introduction

Tuberculosis (TB) has affected humanity since the beginning of time:[1] earlier well-described as consumption and historically causing high morbidity and mortality as the white plague. During the industrial revolution, urban living can be identified as a source of health and nutrition deficiencies and long work hours which facilitated TB transmission. Later progressive socio-economic improvement resulted in a decline in morbidity and mortality.

In 1882, Robert Koch's *Die Aetiologie der Tuberculose*[2] caused a great revolution, clarifying the infectious etiology of the disease which had been in question for so long. The introduction of modern anti-TB drugs in 1944 also contributed to a decrease in mortality in industrialized countries; however, as we will see in this chapter, TB has continued to be an important public health issue on a global scale.

The objective of this chapter is to review the present-day epidemiologic TB situation, and control programs, as well as additional contributing factors such as HIV infection, immigration, and the global economic recession.

### *Causal agent*

*Mycobacterium* is a immobile, aerobic, acid-fast bacteria which is 0.8-4 microns in size, sensitive to solar and ultraviolet light, heat, and disinfectants, but resistant to drying. TB is caused by *Mycobacterium tuberculosis* complex, mainly by *M. tuberculosis*, *M. bovis, M. caprae and M. africanum.* Other mycobacteria, (known as non-TB, atypical or environmental) can also more rarely cause pulmonary or extra-pulmonary pathology.

### *The host*

Host susceptibility is universal, but the risk of infection is directly and mainly related to the degree of exposure. The highest probability of progression to active disease occurs during the first 12-24 months after infection, especially among children, adolescents, the elderly, or immunosuppressed individuals.[3] In countries of high or intermediate TB incidence, the disease more frequently affects children under 4 years of age, followed by young adults. Young adults many times can be smear-positive and transmit the disease to children, who are more susceptible because of their immature immune system. It is also important to note that after 20 years of age, TB tends to affect more males due to higher exposure to infection and higher prevalence of risk factors. In countries where good control programs are in place, incidence among any age group is low and increases slightly with age; in this context, TB is caused by endogenous re-activation, affecting more males and the elderly.

### *Reservoir and source of infection*

An infected person is the reservoir and can be considered a source of infection if active disease occurs. Patients who produce smear-positive sputum are the most contagious, followed by those with positive culture results. It has been documented that even cases with smear and culture negative sputum might also transmit the disease. A correctly treated patient is unlikely to be contagious after 2-4 weeks of treatment. Another source of infection which is of epidemiological interest is the bovine livestock. Other reservoirs also exist but are only of anecdotal interest.

### *Transmission mechanism*

Aerosol transmission plays an important and relevant role in public health. A patient with pulmonary or laryngeal TB produces aerosol contaminants and expulses bacteria which others could inhale, when he or she coughs talks or sings. In industrialized countries, milk pasteurization has made digestive transmission of *M. bovis* anecdotal. Nonetheless, it is important to remember that bovine TB is far from eradicated in cattle, even in some developed countries, and as a consequence, the risk of infection in poor regions continues to be significant. Other transmission mechanisms include cutaneous-mucosal, urogenital, transplacentarial and percutanial inoculation.

### *Natural history of Mycobacterium tuberculosis infection*

Using the "iceberg" epidemiological model, *M. tuberculosis* infection can be separated into infected patients, sick patients and deceased. The sick and deceased patients, or tip of the iceberg, are easily detected, whereas it is difficult to identify the infected patients, which would require testing the entire population. These infected patients represent the hidden and larger part of the iceberg.

A physician can identify TB infection, for example, using tuberculin skin test conversion in the context of contact tracing. Infected patients have the highest probability (about 5%) of developing TB during the first few years after infection (exogenous TB infection), and another 5% could develop TB during their lifetime (endogenous TB reactivation). Therefore, more TB infected individuals means more future TB cases, some with severe clinical forms, such as the TB meningitis. During childhood, a pediatrician plays an important role in the early diagnosis of TB infection and disease, as well as ensuring the compliance of an adequate TB regimen to avoid further complications which could accompany the child throughout his or her life or even result in premature death. In our setting, TB lethality among sick patients must always be under 1%.

### *Epidemiological indicators to evaluate tuberculosis in a community*

The most relevant indicators include: TB incidence, the decrease of this incidence over time, and TB meningitis incidence among children between 0 and 4 years of age. It is also important to use TB infection indicators such as infection prevalence at a specific age and annual infection incidence (AII). In a cohort of tuberculin skin test negative children, a second test must be performed after one year to determine AII. However, this measurement can be difficult to perform and a bias exists for those who are BCG vaccinated, which produces more positive results and hence an inflated AII. To avoid these complications, Styblo defines annual risk of infection (ARI) as the prevalence of infection in two cohorts of the same age during consecutive years. ARI is determined by calculating the decline and prevalence of the last year, which should be the same as the AII. Styblo also estimated that 8-12 infected cases would arise from one smear-positive TB case, even though a recent study reduced this approximation to 2.6-5.8 because of improved TB control.[4]

### *Disease burden in the world and control plans*

Despite the wealth of knowledge about the disease's natural history and the availability of adequate drugs to cure the majority of patients, TB continues to be a global public health problem and the second most common cause of death by an infectious agent in the world, following HIV.[5] The last WHO report estimated that more than 9 million cases occurred worldwide in 2008, with an incidence of 139 cases per 100,000 inhabitants (Fig. 1), just under that of 2007. The majority of these cases are reported in Asia (55%) and Africa (31%) and one half of the total cases occur in 5 countries: India, China, Indonesia, Nigeria and South Africa. Of the total newly diagnosed cases, four million are smear-positive (incidence of 61/100,000) and almost one and a half million are infected with HIV (80% live in Africa).[6,7] Even though the absolute number of cases is increasing with the rising total population, the global incidence rate began to decrease in 2004, with an annual decline of less than 1%.

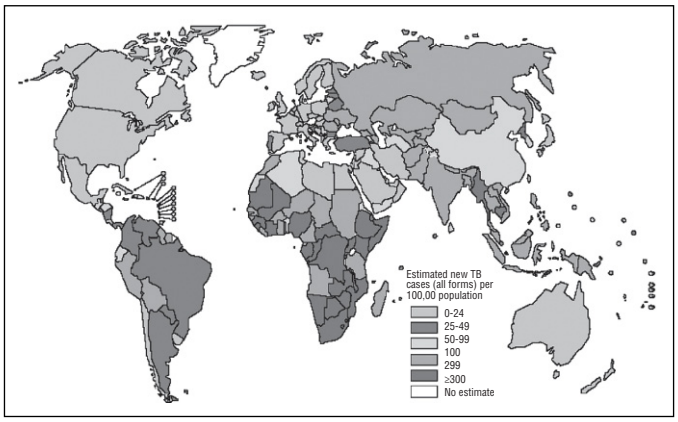


**Figure 1.** Estimated tuberculosis (TB) incidence rates, 2008.

This pattern was also observed with HIV prevalence in Africa. Of the 6 WHO regions, TB incidence is decreasing in five, with the exception of the European region, where it remains stable. There are more than a half million estimated cases of multi-drug resistant (MDR) TB, 56% of which are newly diagnosed cases and 70% are smear-positive. The 5 countries with the highest number of MDR TB cases are India, China, the Russian Federation, South Africa and Bangla Desh.[8,9] In 2007, TB mortality was estimated at 19/100,000 habitants, with 1.3 million non-HIV deaths and almost 1.5 million HIV infected deaths.

In the WHO European region, almost one half million cases were reported (incidence 52/100,000) in 2008, comprising 6% of the reported cases in the world. Incidence was increasing until 2004 but decreased by 2.5% last year and it is still early to predict whether this tendency will continue. Notification rates and mortality increase following a west to east gradient. Eighteen countries have been defined as High Priority Countries (HPC)*. These countries all present incidences over 100 cases/ 100,000 inhabitants, represent more than 80% of the TB cases in the region and report rates more than 6 times higher than those of the European Union. The percentages of MDR TB cases among new diagnoses and previously treated cases are 14% and 50%, respectively, in HPC. Extensively multi-drug resistant (XDR) TB prevalence is around 1.4%. The number of HIV infected TB patients has doubled since 2006 in HPC. This trend has only been observed in the HPC and it is assumed to be associated with improved detection of co-infected TB.[10] Treatment outcome among new cases is also not good, with a success rate of 70%. Low treatment adherence, an elevated proportion of MDR TB and an increasing proportion of HIV co-infected patients all contribute to this poor result. Surveillance data in the region demonstrate diverse epidemiological trends, with the disease burden concentrated in the 18 HPC, which is truly worrisome.[10]

In European Union and European Economical Area countries, more than 80,000 cases were detected in 2008. Incidence was 16.7 cases/100,000 inhabitants, which was 1% lower than in 2007. In the EU, incidence has been steadily declining in the last 5 years. Rates less than 20/100,000 have been reported in 21 countries, but high rates remain in Romania (115), the Baltic countries (between 33 and 67), Bulgaria (41), Portugal (28) and Poland (21). Twenty three percent of the reported cases were immigrants, ranging from 20-88%. Six percent of the reported cases with available drug susceptibility results present a MDR resistance pattern and 90 cases of XDR TB were reported.[11]

Spain reported one of the highest numbers of cases of EU in 2008 (third after Romania and Great Britain), with an incidence of 18.4/100,000 and 30% immigrants.[12] Knowledge of TB epidemiology in our country is far from optimal, especially regarding important factors such as HIV co-infection and drug resistance.[10,12] Program evaluation indicators are also not available on the national level. Two years ago in Spain, a national TB control program was created to improve program coordination between each autonomous community and to enforce disease surveillance and control. However, it does not appear to have reached the initial expectations.[13]

Only 3 countries have achieved the successful treatment rate defined by the WHO objective and many countries report a rate under 85%, usually because of lack of information. Some countries, such as Spain, do not even report it. Even though an unknown treatment result does not necessarily represent a negative result, the absence of such important information complicates TB control planning.[14] The TB epidemiological situation in the EU is heterogeneous; the poor evolution of TB incidence in high or intermediate burden countries requires their close follow-up. The quality of reported information, with respect to important indicators such as absolute number of cases, drug resistance and treatment outcome, is poor and complicates the control of the disease. It is also important to note that the disease is affecting vulnerable populations within low incidence countries, such as immigrants and the poor.[15,16]

## Have there been changes in the site of tuberculosis? Epidemiological significance of extrapulmonary tuberculosis

Pulmonary TB is always the most frequent, even though extrapulmonary (EP) forms have increased its frequency in recent years among HIV infected patients and even more recently among distinct groups of immigrants. EP TB is a clinical problem rather than a public health problem, since isolated non-pulmonary disease is not contagious. However, between 6% and 20% of patients with EP TB also have active pulmonary infection.[17-20] In addition, about 20% of patients with EP disease may have a positive sputum culture and 40% of them a positive sputum smear, even in the presence of normal or non-suspicious chest X-ray findings.

Several studies from European, North American and Asian countries in the last decade indicate that between 12% and 53% of TB patients present with a major form of EP TB. The variability of EP TB depends not only on the prevalence of well-characterized risk factors among the population, but also on the definitions. For example, patients with concomitant pulmonary involvement, intrathoracic lymphadenopathy, pleurisy or miliary disease may or may not be included.[21-29] Longitudinal studies performed in industrialized countries have shown that the proportion of EP cases has remained stable or increased over time due to a disproportionally slower decrease in EP rates as compared to pulmonary TB[18,24,25] This may be explained in part by the growing number of individuals of a non-European ethnic background living in industrialized countries. However, a different dynamic of disease reactivation, in which EP forms are favored over time since infection, may also be involved. Although TB control is improving, clinicians should be aware of this trend in order to accurately diagnose EP TB among both specific high-risk groups and the native population.

Characterized risk factors for EP TB include a young age, female gender, non-European ethnic background and immunosuppression from HIV infection, end-stage renal disease, liver cirrhosis,[17-20,22-29] and probably anti-TNF therapy[30] and solid organ transplantation.[31] Conversely, classic TB risk factors, such as diabetes mellitus, alcoholism, homelessness, incarceration, smoking, previous TB history and previous contact with a TB patient, are associated with pulmonary presentation rather than EP disease.[18,19] Although literature is limited, strains isolated from EP TB cases seem to belong

* Armenia, Azerbaijan, Bielorrusia, Bulgaria, Estonia, Georgia, Kazakhastan, Kyrgyzstan, Letonia, Lituania, Moldavia, Rumania, Rusia, Tajikistan, Turquia, Turkmenistan, Ucrania, Uzbekistan

less frequently to cluster[18] and MDR strains than those from pulmonary cases.[19] One study demonstrated that the time from migration to TB diagnosis was almost double for EP cases compared to pulmonary cases (45 vs 24 months)[25] and within an endemic region, the time elapsed since contact with a contagious case to diagnosis was significantly longer for EP cases (<5 years for 23% of cases) than pulmonary cases (<5 years for 73% of cases).[17] Several polymorphisms in some genes have also been associated with EP TB.[32-36] However, the number of EP TB cases that are explained by these polymorphisms or their relationship to predisposing ethnic factors is unknown. Finally, some strain characteristics, such as belonging to the W-Beijing family[37] or certain phosfolipase-C gene D *(plcD)* mutations are associated with EP disease.

The most common sites of EP TB are the lymph nodes and pleura, although significant differences of frequency are observed by age, gender, ethnic background and immunosuppressant conditions. Nonetheless, some classic associations still hold true, such as predominance of intrathoracic lymphatic disease, higher frequency of meningitis in children under 15 years of age, absence of genitourinary TB before 35 years of age and the predilection of pleurisy for older teenagers and young men. Lymphatic TB has been repeatedly associated with ethnic backgrounds other than white European, osteoarticular TB appears to be more frequent in sub-Saharan Africa and peritonitis is more frequent in North Africa and Asia.[25-27]

## Tuberculosis prevention and control programs

The present global TB control strategy was started during the 90's, when TB incidence and mortality continued to increase. The WHO created the "Directly Observed Treatment, Short Course" (DOTS) strategy, which requires each country to detect smear-positive TB cases and offer standardized DOT , with the objective of curing over 85% of TB patients.[7] DOTS has been implemented in 180 countries and it has cured an estimated 25 million patients (Table 1).[6,38]

**Table 1**
Components of "Directly Observed Treatment, Short Course" (DOTS) strategy

| |
|---|
| Political commitment with increased and sustained financing |
| Case detection through quality-assured bacteriology |
| Standardized treatment with supervision and patient support |
| An effective drug supply and management system |
| Monitoring and evaluation system and impact measurement |

Despite these advances, TB has continued presenting new challenges on a global scale. In 2006, the TB Alliance created the Global Plan to Stop TB during 2006-2015. This strategy is the WHO-recommended approach to reduce TB burden. The principle components of the strategy include:

- Pursue high-quality DOTS expansion and enhancement.
- Address TB/HIV, MDR-TB and the needs of poor and vulnerable populations.
- Contribute to health system strengthening based on primary healthcare.
- Engage all care providers.
- Empower people with TB and communities through partnership.
- Enable and promote research.[39]

Therefore, the global TB control objectives have been re-defined to detect 70% of new smear-positive cases and to cure at least 85% of them. TB incidence should start to decrease by 2015 and TB prevalence and mortality should decrease by half by 2015 as compared to figures from 1990. Various activities centered around DOTS were outlined to achieve the Stop TB Global Plan objectives. The 70% detection and 85% cure rates will decrease the number of infectious TB cases and TB-infected contacts, thus decreasing disease burden and mortality. According to estimations from epidemiological parameters obtained in developed countries (average ARI and risk of disease development by primary infection, re-infection or reactivation), the goal of the proposed objectives is to decrease TB incidence to at least 5-10% per year, if no other event associated to greater risk of disease progression, such as HIV infection, occurs.

Nonetheless, interventions directed at increasing the quality of health and life in general, such as better housing, better nutrition or reducing smoking, will also influence infection transmission and the risk of disease progression, independent of DOTS implementation. In fact, in an analysis of the impact of specific activities for TB control compared to general country development factors (improved healthcare, economic growth, etc), better TB evolution was explained mainly by improved socio-economic development in most coutries.[40,41]

Though the Global Plan calls for the coalition of various organizations to present diverse interventions which can be implemented, much criticism has been made about its difficulty.[42] Some challenges include to sustain the political commitment, the competition with other priorities, the threat of HIV, the quality of patient management to prevent drug resistance, to build human resources capacity, to improve the quality of diagnostic and to foster operative research.[43] Furthermore, the adaptation of field activities and quality of information must also be taken into account. The use of the appropriate strategy requires full knowledge of the local TB situation, an adequate evaluation system of control activities and a functioning surveillance system.[44] In high TB burden countries, considerable uncertainty exists about the indicators used to measure progress towards Global Plan objectives.[45]

In low burden countries, TB disproportionately affects vulnerable populations (immigrants, homeless, etc), which complicates case management (poor treatment adherence, increased drug resistance), requires additional professional training, and can increase diagnostic delays and disease advancement.[46] In Spain, the decrease in TB incidence has been accompanied by a change in the epidemiological profile, especially in large cities such as Barcelona, where the proportion of immigrant cases has reached up to 50% (Fig. 2).[47] Similarly, highest incidence rates among native patients are found among the elderly, demonstrating improved disease control (Fig. 3). The city control program has incorporated the use of Community Health Workers to support immigrants in treatment adherence and contact tracing, and to act as facilitators during communication with the healthcare system.[47,48] However, program development with respect to surveillance and TB control is uneven in each Autonomous Community in Spain, even though organizational models do exist, such as in Galicia, which produce positive results and considerable decreases in TB incidence.[49,50]

Another aspect to consider in a low burden setting is the absence of clinical suspicion in the presence of compatible symptoms. From a public health perspective, this increases diagnostic delays, time for transmission and the possibility of epidemic outbreaks especially affecting children.[51] One study performed on 1,000 pediatric active TB cases in Barcelona from 1987 to 2007, the index case was identified in almost half (478) of the cases. The same study describes the outbreaks reported from 2000 to 2007 and states that 75 of the 219 outbreaks (34%) involved children. The 98 secondary cases under 15 years of age represented half of the pediatric TB cases in that period.[52]

As demonstrated, there is much knowledge about this old disease in the world and about the complications that exist to decrease its impact. The Global Plan to control TB should serve as a stimulant to

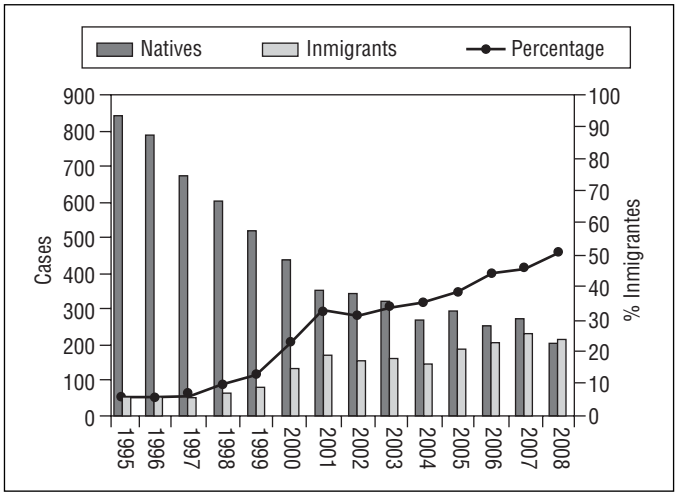


**Figure 2.** Evolution of tuberculosis by origin country. Barcelona, 1995-2008.

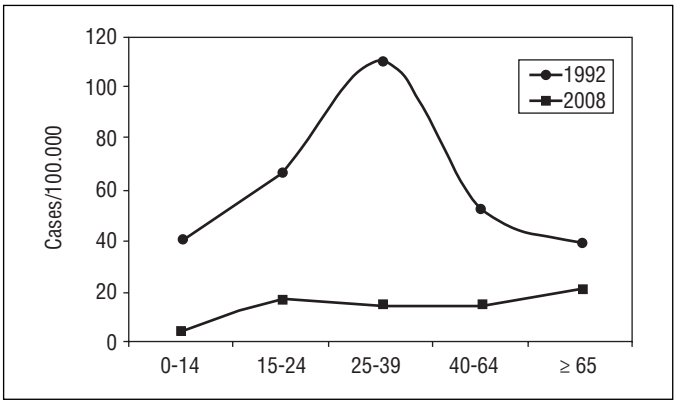


**Figure 3.** Incidence by age-groups in natives. Barcelona, 1992-2008.

decrease the burden of suffering and economical loss that is represented by TB, and also to direct us to the elimination of TB as a public health problem by 2050.[39] It can also contribute to other initiatives, such as the Lancet TB Observatory, which will assess and monitor the progress in TB control and research, assess domestic and global financing, regularly disseminate information and advocate for intensified efforts with stakeholders at all levels.[53]

## Conflict of interest

The authors declare they have not any conflict of interest.

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