



## Study of Central Nervous System Tuberculosis over a Decade, 2003-2012. Immigration and Drug Resistance

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### Abstract:

#### Introduction:

Central nervous system tuberculosis (CNS-TB) is uncommon but is among the most severe presentations of tuberculosis. We studied CNS-TB over 10 consecutive years (2003-2012) at Basurto University Hospital (Spain).

#### Methods:

This was a retrospective descriptive study of all patients diagnosed with CNS-TB between 1 January 2003 and 31 December 2012. We analysed epidemiological, clinical and microbiological characteristics of the disease, the association between TB and HIV, treatments including adverse effects and resistance, mortality, sequelae and migrant status. The study was approved by the hospital's Ethics and Research Unit.

#### Results:

Out of 526 patients with TB, 23 (4.3%) were diagnosed with CNS-TB. Of these, 39% were foreign born, none were <20 years of age, and half were HIV positive. The mortality rate was 22%-30%. The most common symptoms were fever (60%) and altered consciousness (60%); 39% of patients had TB at another site, 78% had tuberculous meningitis and 95% had elevated cerebrospinal fluid adenosine deaminase levels. Overall, 83% received quadruple therapy. Two foreign-born individuals relapsed. No drug resistance was observed.

### KEYWORDS

Tuberculosis.  
Central Nervous System.  
Tuberculosis.  
Multidrug-Resistant.  
Human Migration.

**Conclusions:**

Overall, CNS-TB accounts for 4.3% of TB cases, tuberculous meningitis being the most common form. No cases were observed in children. Patients with TB including CNS-TB should undergo HIV serological screening.

A disproportionate number of cases of CNS-TB occur in immigrants and hence they should be a target population for improving TB control in our setting. It is important to identify patients' place of origin, to ascertain the prevalence of TB and level of drug resistance there, as this information might influence their management.

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**PALABRAS CLAVE**

Tuberculosis.  
Sistema Nervioso  
Central.  
Tuberculosis.  
Multirresistente.  
Migración Humana.

**Estudio de la neurotuberculosis década 2003-2012. Inmigración y fármaco resistencia.****Resumen:****Introducción:**

La afectación tuberculosa del Sistema Nervioso Central o Neurotuberculosis (NTB), aunque poco frecuente, es una de las presentaciones más graves de la enfermedad tuberculosa (TB). Se realiza el estudio de la NTB durante 10 años consecutivos (2003-2012) en el Hospital Universitario Basurto Bilbao (España).

**Métodos:**

Estudio descriptivo retrospectivo, de todos los casos de NTB diagnosticados desde el 1 de enero del 2003 al 31 de diciembre del 2012. Se analizan las características epidemiológicas, clínicas, microbiológicas, la asociación TB-VIH, tratamientos con sus efectos secundarios y resistencias a los mismos, mortalidad, secuelas de la infección y la relación con la inmigración. Este estudio cumple con todos los permisos y requisitos de la Unidad de Investigación y Ética de este Centro.

**Resultados:**

Se diagnosticaron 23 pacientes con NTB (4,3%) de un número total de 526 con TB. De estos el 39% eran extranjeros. No hubo ningún caso en menores de 20 años. El 50% de NTB eran VIH positivos. Los síntomas más frecuentes fueron fiebre 60% y alteración del nivel de conciencia 60%. El 39% presentaban NTB y TB en otra localización. El 78% tenían TB meníngea. La adenosina deaminasa (ADA) en líquido cefalorraquídeo fue positiva en el 95%. El 83% de los pacientes se trataron con cuádruple terapia. Presentaron recidiva 2 pacientes extranjeros. No se registraron resistencias farmacológicas.

**Conclusiones:**

La NTB representa el 4,3% de los pacientes con TB, el cuadro clínico más frecuente es la TB meníngea. No se registró ningún caso pediátrico. En los pacientes con TB, incluida NTB, se debe realizar siempre serología VIH.

Los inmigrantes aportan un número importante de casos de NTB, por ello son la población diana para la mejora en el control de la TB en nuestro entorno. Es importante valorar la procedencia del paciente para conocer la prevalencia de TB y la fármaco resistencia del país de origen, ya que son de ayuda en el manejo de la NTB.

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**GILTZA-HITZAK**

Tuberkulosia.  
Nerbio-sistema  
Zentrala.  
Tuberkulosia.  
Multirresistentea.  
Giza migrazioa.

**Neurotuberculosisaren azterketa 2003-2012 hamarkada. Immigrazioa eta sendagaien aurkako erresistentzia.****Laburpena:****Sarrera:**

Sistema Nerbiooso Zentraleko tuberkulosia edo Neurotuberkulosia (NTB) nahiz eta oso gutxitan eman, gaixotasun tuberkulosoaren (TB) aurkezpenik larriena da. Basurtuko Unibertsitate Ospitalean 10 urtetetan (2003-2012) emandako NTB kasuen azterlana aurkezten da.

**Metadoak:**

2003ko urtarrilaren 1etik 2012ko abenduaren 31era arte emandako NTB kasuen azterketa deskribatzaile atzerakoia. TB eta GIBaren arteko harremana, hilkortasuna, tratamenduen ondoriozko efektuak eta erresistentziak, infekzioaren ondorioak, inmigrazioarekiko harremana eta ezaugarri epidemiologiko, kliniko eta mikrobiologikoak aztertzen dira. Azterlan honek zentro honen Azterketa eta Etika Unitatearen baimen eta baldintza guztiak betetzen ditu.

**Emaizak:**

TB zuten 526 gaixoetatik 23k NTB zuten ( % 4.3).Hauetatik %39 atzerritarra zen. Ez zen 20 urtetik beherako gaixorik ikusi.NTBa zuen %50 GIBa zuen. Sintomarik ohikoenak sukarra (%60) eta konorte mailaren aldatzea ( %60) izan ziren. 39% NTB eta TB zuen beste koka-pen batean. %78 meningeetako TB zuen. Adenosiona deaminasa (ADA) likido zefalorrakidean %95 kasuetan positiboa izan zen.Gaixoen %83 lau farmakoekin tratatu zen. 2 atzerritarrek berrerotzea aurkeztu zuten. Ez zen farmakoekiko erresistentziarik erregistratu

**Ondorioak:**

TB duen %4.3k NTB du, TB meningeoa koadro kliniko ohikoena izanik. Ez zen kasu pediatrikorik erregistratu.TB kasu guztietan , NTB barne, beti GIBerako serologia egin behar da. Atzerritarrak NTB kasu guztien kopuru garrantzitsua dira, horregatik gure inguruko TBaren kontrolaren hobekuntzarako xede- biztanleria izan behar dute.

Garrantzitsua da gaixoaren jatorria jakitea, TBaren prebalentzia eta herrialdearen farmako-erresistentzia ezagutzeko , NTBaren ezagupenenerako ezinbestekoak izanik.

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**Introduction**

Tuberculosis is one of the infectious diseases responsible for the highest levels of morbidity worldwide and a significant level of mortality in developing countries. A third of the world's population is infected with tuberculosis. Each year, millions of people die from TB across the world, and together with HIV, it is one of the leading causes of death worldwide<sup>1</sup>.

Tuberculosis is present all over the world, but its prevalence, opportunities for accessing early diagnosis and treatment, mortality rates and levels of drug resistance differ substantially between regions. Over the last decade, in our region, there has been a significant increase in migratory flow. This has involved movement of people from countries with a high prevalence of TB to others with a low prevalence. In the 1970s to 1990s, studies in countries such as the United States of America and Canada noted a decline in the control of TB. They observed that while the incidence of the disease had a downward trend in the native population, there was an upward trend in immigrants. For this reason, they concluded that the control of TB in immigrants was a priority<sup>2-4</sup>.

The 2017 WHO global tuberculosis report stated that 6.3 million new cases of TB were reported in 2016. A total of 476,774 cases reported were in HIV-positive people, and of these, 85% were on antiretroviral therapy. Overall, 6.9% of the new cases of TB were in children (<15 years old).

One of the most severe presentations of tuberculosis is central nervous system tuberculosis (CNS-TB)<sup>5</sup>. It accounts for 1% of all cases of TB and 10 to 15% of the extrapulmonary forms of the disease. Early diagnosis is sometimes difficult given that the disease manifests in various different non-specific ways. The most common clinical presentation is tuberculous meningitis.

The risk of developing CNS-TB is higher in children under 5 years of age, individuals with HIV infection, and those in an immunosuppressed state: transplant recipients and patients receiving corticosteroids, chemotherapy or anti-TNF therapy. Neonatal vaccination with the Bacillus Calmette–Guérin (BCG) vaccine is effective against CNS-TB as well as miliary TB. Notably, CNS-TB is

associated with a high rate of mortality and sequelae are relatively common, both increasing with delays in diagnosis and treatment.

The treatment of CNS-TB is similar to that of pulmonary tuberculosis but longer, lasting for 7 to 10 months (versus 6 months for pulmonary tuberculosis). It is based on four different drugs, rifampicin, isoniazid, pyrazinamide and ethambutol, for 2 months, followed by two others, isoniazid and rifampicin, to complete the 7 to 10 month treatment period. If a strain is confirmed to be sensitive to the first three drugs, ethambutol can be withdrawn, continuing with the other three drugs for the first 2 months<sup>6</sup>. Corticosteroids reduce the rate of mortality associated with CNS-TB but not the neurological sequelae<sup>7,8</sup>.

This study investigated cases of CNS-TB over a period of 10 consecutive years (2003-2012) in Basurto University Hospital, in Bilbao, a city in the north of Spain, to determine the incidence and characteristics of this disease and its relationship with immigration and drug resistance. The study period coincides with marked growth in immigration.

**Materials and methods**

This is a retrospective descriptive study of all the cases of CNS-TB, including children, diagnosed between 1 January 2013 and 31 December 2012 in Basurto University Hospital in Bilbao. This hospital is the main referral hospital for the Bilbao health district and has a catchment population of 350,000 people, of whom 8.5% are foreign born. Postcodes were used to identify the distribution of cases in terms of place of residence.

Data were drawn from the medical records of 23 patients hospitalised during the study period with a diagnosis of CNS-TB. This study received approval from the hospital's Research and Ethics Unit, was conducted following the corresponding protocol and met all applicable requirements. Cases of tuberculosis were defined following the definition of the European Centre for Disease Prevention and Control (ECDC), which includes previous definitions of the Multicentre Project for Tuberculosis Research (MPTR)<sup>9,10</sup>.

### Data processing

The information obtained from patient health records were entered into a database designed in FileMaker. Data were subsequently exported as text files and directly imported into the software to be used for processing.

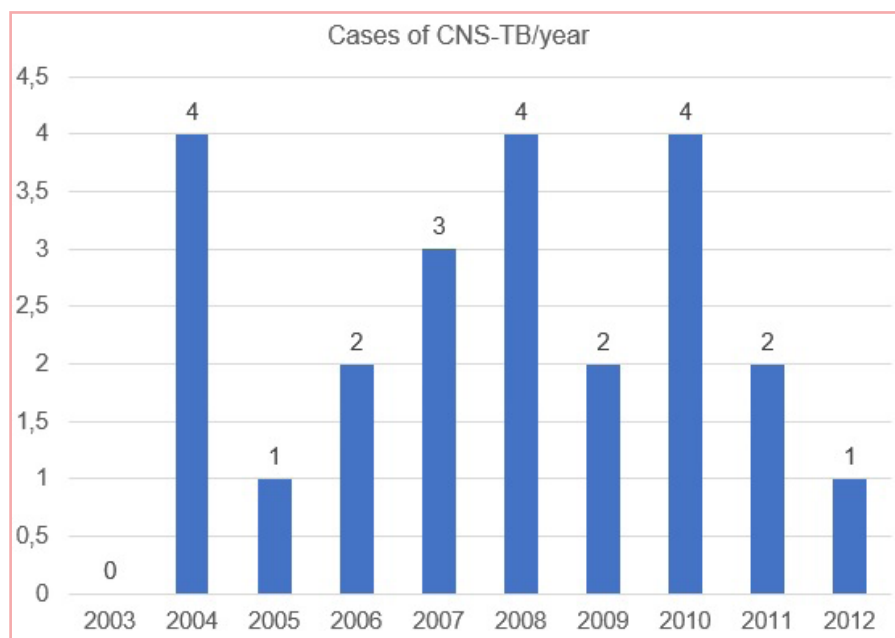
### Statistical Analysis

Data mining was carried out in the R environment on a Linux Operating system, OpenSuSE 3.1. Specifically, the Hmisc package was used for performing calculations and plotting statistical graphs<sup>11,12</sup>.

### Results

Between 2003 and 2012, 23 patients were diagnosed with CNS-TB. We reviewed health records of 526 patients

who met criteria for TB<sup>13</sup>, of which 4.3% were cases of CNS-TB. Among these, 61% of patients were male and 39% female, yielding a sex ratio of 1.5:1. The age range with the most of cases of CNS-TB was 40-49 years, with none in patients under 20 years of age. Notably, 61% of cases were in individuals born in Spain. Among the 39% of cases in foreign-born individuals, the most common place of birth was South America (44%), mainly Bolivia. The time distribution of CNS-TB cases is shown in Figure 1, with a maximum of 4 cases per year. Notably, foreign-born individuals accounted for 31% of cases of all types of TB diagnosed in Basurto University Hospital (n=526) and 39% of the CNS-TB cases, this indicating that the immigrant population contributes substantially to the incidence of CNS-TB in the study setting.



**Figure 1.** Number of cases of central nervous system tuberculosis (CNS-TB) per year.

The overall rates of TB vary depending on whether the population studied is native or foreign, the prevalence being higher in foreign-born individuals. Table 1 shows the rates of all TB, including CNS-TB, per 100,000 people/year overall and in Spanish and foreign-born individuals in Bilbao for 2003 to 2012.

Half of the patients with CNS-TB were HIV positive, other patients having negative or unknown HIV status. In contrast, among the patients with TB excluding CNS-TB, only 26% were HIV positive. We assessed whether the HIV-positive patients met the criteria for AIDS, and among those who did, the diagnosis was made due to TB in 42% of cases. The rate of mortality due to CNS-TB during the first hospitalisation was 22%, the rate rising to 30% if we consider deaths associated with

subsequent hospitalisations for complications related to TB. These rates are much higher than overall mortality rates for TB, which are 6% during the first hospitalisation and 8% considering subsequent hospitalisations due to TB-related complications.

Notably, 87% of patients were hospitalised through the emergency department. Considering patient place of residence, the most deprived districts had the highest number of cases of CNS-TB.

Suspected TB was diagnosed in 30% of patients after an initial assessment, taking a clinical history and performing basic complementary tests (blood tests, radiological examination). In 43% of cases, TB was not suspected at this stage and in 26% of cases, there was clinical suspicion of a different condition.

Year	Cases of TB /year	Overall rate /100,000 residents	Rate in Spanish-born individuals /100,000 residents	Rate in foreign-born individuals /100,000 residents
2003	65	18.3	16.6	54
2004	68	19.3	14.1	122
2005	59	16.7	13	86.3
2006	49	13.8	10.7	56
2007	61	17.2	12	91.3
2008	54	15.2	9.1	92
2009	39	10.9	6.1	60.7
2010	53	15.0	10.4	64.4
2011	43	12.1	7.4	60.2
2012	36	10.2	5.8	56.3

**Table 1.** Rate of tuberculosis (TB) per 100,000 residents overall and in Spanish and foreign-born individuals in Bilbao 2003-2012.

The health records of 21 patients reported whether or not they had a history of TB. Of these, 86% had no history of TB while this information was missing for 14% of patients. Information concerning whether patients had been in contact with people infected with tuberculosis was reported in the health records of 10 patients, 9 having no history of contact and 1 reporting contact. Regarding substance use, 35% of patients with CNS-TB were smokers, 30% were addicted to parenteral drugs and 18% reported moderate or excessive alcohol intake.

Regarding the clinical presentation of CNS-TB, the most common symptoms were: fever (60%), altered level of consciousness (60%), constitutional syndrome with weight loss (39%), asthenia (34%), anorexia (34%) and headache (21%). The most common conditions associated with CNS-TB were: liver disease (24%), HIV (33%), AIDS (10%) and psychiatric illnesses (10%). Notably, 39% of the patients also had TB at another site, mainly pulmonary and miliary tuberculosis, and 78% had tuberculous meningitis, while 21.7% of patients had tuberculomas or tuberculous brain abscesses.

Adenosine deaminase levels in cerebrospinal fluid were elevated (>10 U/L) in 95% of patients. Microbiological analysis using microscopy and culture techniques was performed in 32 samples of cerebrospinal fluid. A total of 8.6% of cases were acid-fast bacilli positive and 8.6% of cultures were positive.

All patients with CNS-TB underwent chest X-rays. In half of them, the results were classified as normal, while in the other half, the imaging revealed signs of disease

including pulmonary infiltrates, cavities, lymph node or miliary involvement. There was bilateral pulmonary involvement in 43% of cases.

All the patients received anti-tuberculosis drugs, 83% of them being given quadruple therapy and the others (17%) triple therapy. Two foreign-born patients, one from Bolivia and the other from Ecuador, relapsed. No cases of resistance to the anti-tuberculous treatment were reported.

### Discussion

This study assessed CNS-TB during the period 2003-2012, a decade that saw an increase in immigration in our region. This was a retrospective study with the intrinsic limitations of this type of research approach. Data were obtained from the health records of patients diagnosed with tuberculosis during the study period, that is, we were only able to retrieve what was in the health records and did not obtain further information. Additionally, there were very few cases (n=23).

In our study, we observed that 4.3% of patients with TB had CNS-TB, this rate being higher than that found in previous studies<sup>14</sup>. We did not find any cases of CNS-TB in patients younger than 20 years of age, despite children usually being more vulnerable to CNS-TB<sup>5,16</sup>. This may be attributable to the BCG vaccine, which was on the child vaccination schedule here from the 1950s until 2013, it having been suspended in other regions of Spain in 1991. Several systematic reviews and meta-analyses have concluded that BCG vaccination protects

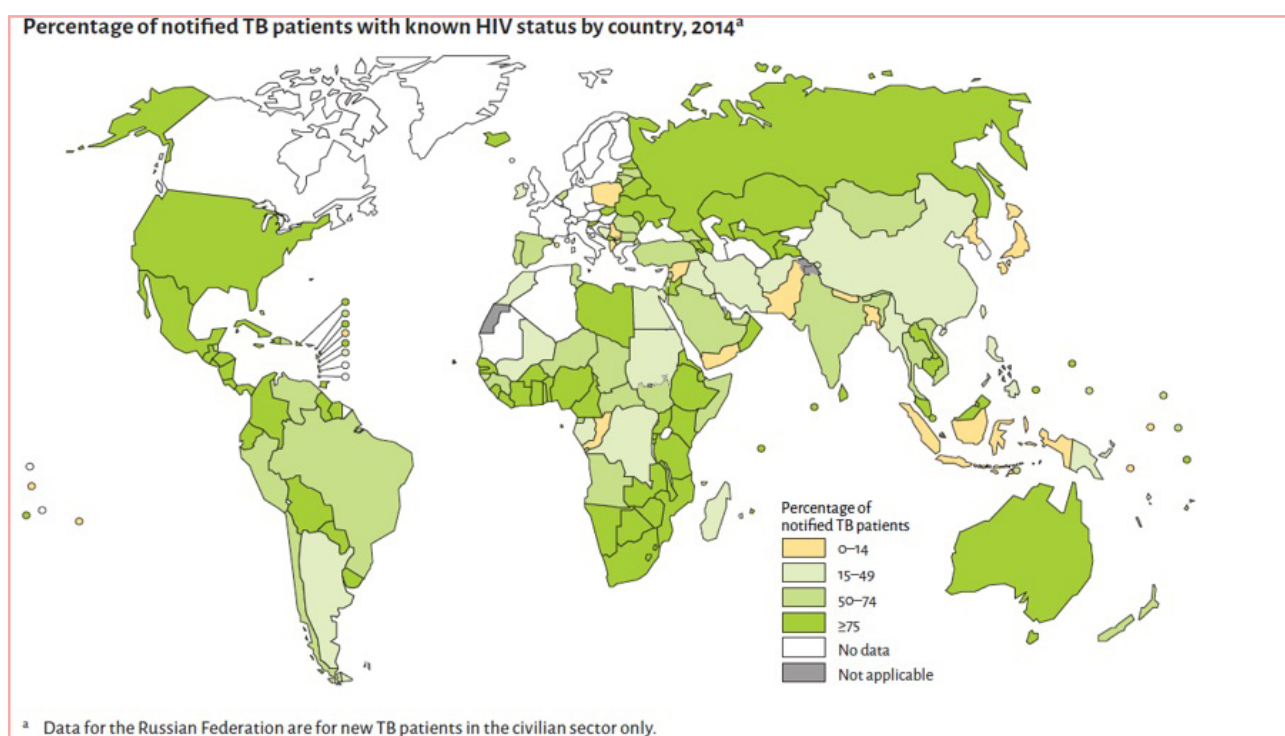


against meningeal and military types of TB and estimated that this protective effect lasts for at least 10 years. Currently, vaccination against tuberculosis is only indicated in high-risk patients<sup>17</sup>.

Immigrants represent a disproportionate percentage of patients with CNS-TB (39% versus only 8.5% of the general population in the geographical region studied). Further, there are large differences in the rate of tuberculosis between native and foreign-born people. For example, in the population studied in 2012, the rate of TB among foreign-born people was 56.3/100,000, much higher than the rate of 5.8/100,000 observed among those born in Spain. With immigration, there has been an influx of people from countries with a high

prevalence of TB to other countries with a low prevalence<sup>18</sup>. Often, cases of tuberculosis in immigrants from other countries with a high prevalence of the disease are due to reactivation of imported latent TB infection. These tend to occur within the first 5 years after arrival in the host country. For this reason, immigrants should be a target population for efforts to improve our control of TB.

CNS-TB has a high mortality rate and a notably higher rate of major sequelae than TB at other sites. Further, patients with this type of tuberculosis are more likely to be HIV-positive than patients with tuberculosis overall<sup>5</sup>. Worldwide, the association between TB and HIV infection is an important health problem (Figure 2).



**Figure 2.** Patient HIV status in notified cases of TB, 2014. Source: World Health Organization.

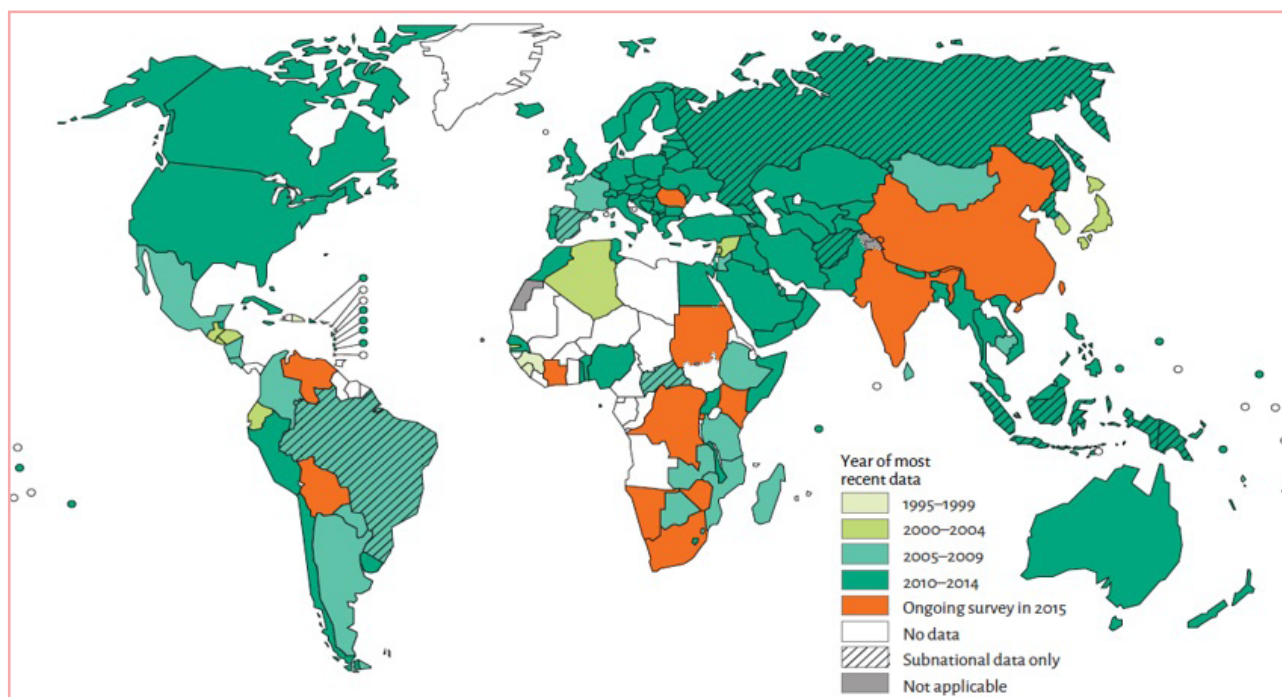
These two diseases are often found in combination since immunosuppression in HIV patients favours tuberculosis infection and reactivation. Additionally, it is important to know the immunological status of HIV-positive patients, since it influences the choice of regimen for highly active antiretroviral therapy (HAART)<sup>19</sup>. This is of particular importance when TB and HIV infection are diagnosed simultaneously: HAART should be started at 2 to 4 weeks if the HIV infection is advanced and at 8 to 12 weeks if the patient is not at an advanced stage of the disease<sup>20</sup>. In patients with HIV infection and tuberculous meningitis, HAART should be delayed, given that early initiation is associated with numerous severe adverse effects and does not improve the course of the disease<sup>21</sup>. For this reason, all patients diagnosed

with TB, including CNS-TB, should undergo serological testing for HIV, given the implications of HIV control for the course of CNS-TB.

Most patients with CNS-TB were hospitalised through the emergency department (87%). The most common presentation was tuberculous meningitis. To achieve early diagnosis, we require a high level of suspicion, based on epidemiological, clinical, analytical (cerebrospinal fluid, ADA), microbiological and radiological findings. If we suspect CNS-TB, treatment with quadruple therapy should be started, without waiting for the microbiological confirmation of the diagnosis, given that *Mycobacterium tuberculosis* grows slowly and the culture result may require 6 to 8 weeks. It is important to identify patients' place of origin, and if

they are foreign born where they were born, in order to ascertain the prevalence of TB and the level of drug re-

sistance there, as this information might influence their management (Figure 3).



**Figure 3.** Surveillance data on TB drug resistance 1994-2015. Source: World Health Organization.

### Conclusions

In our region, CNS-TB represents 4.3% of all cases of tuberculosis and the most common form is tuberculous meningitis. We did not observe any cases in children. The incidence of CNS-TB in HIV-positive patients is high. In patients with TB, including CNS-TB, we must always perform serological testing for HIV, given that the control of HIV is very important for improving the course of CNS-TB. Additionally, the decision on when to start antiretroviral treatment varies depending on patient immunological status. Immigrants account for a relatively high percentage of cases of CNS-TB, and for this reason, they should be the target population for seeking to improve the control of TB in our setting. We only observed cases of relapse in foreign-born patients. We did not observe any cases of CNS-TB with drug resistance. It is very important to identify the place of origin of the patient to assess the prevalence of TB and the level of drug resistance in the country of origin.

### Conflict of interests

Authors do not have any conflict of interest to declare.

### Sources of funding

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