Estimation of tuberculosis mortality burden in Spain: a review of the major data sources

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Although the TB mortality rate in Spain is decreasing, it is still necessary to continue improving prevention, diagnosis and treatment of TB https://bit.ly/3N4v8fC

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Abstract

Introduction In Spain, notifications of cases of tuberculosis (TB) are registered through the National Epidemiological Surveillance Network (RENAVE). The Minimum Basic Data Set (CMBD) provides information on hospital discharge and the National Statistics Institute (INE) draws on medical death certificates. This study aimed to describe TB mortality in Spain and to compare estimates across data sources, as well as with EU/EEA countries.

Material and methods A retrospective study of TB data between 2008 and 2021 was performed. Mortality rates (MRs) were calculated for the three databases as well as case fatality rates (CFRs) for TB location and HIV status using RENAVE data. Time trends were calculated and the mean MR and annual mean percentage change for Spain were compared with EU/EEA countries.

Results Between 2008 and 2021, 4127 TB deaths were reported to RENAVE, 3877 to INE and 4775 to CMBD. The MR was 0.62 per 100 000 inhabitants for RENAVE, 0.59 for INE and 0.72 for CMBD. A statistically significant downward annual trend was observed. Highest MRs across all databases were found in men and in those over 80 years old. CFR was higher for meningeal TB and for HIV patients with a risk ratio of 2.02 (95% CI 1.82–2.2; p<0.05).

Conclusion Although the TB MR in Spain has followed a downward annual trend, it is necessary to continue improving prevention, diagnosis and treatment. This will require comprehensive measurement, better knowledge and better use of all information to complement surveillance systems.

Introduction

Tuberculosis (TB) is a disease caused by the bacillus *Mycobacterium tuberculosis* that mainly affects adults worldwide [1]. It is the world's leading infectious cause of death, only recently surpassed by COVID-19 [2]. Several risk factors for TB mortality have been identified: age, male sex, HIV co-infection, comorbidities (especially diabetes mellitus), drug resistance and disease severity. Other factors including late diagnosis, irregular treatment, extrapulmonary TB (EPTB), and alcohol and drug use have also been associated with TB mortality [3].

The World Health Organization (WHO) estimates that in 2022 there were 10.6 million new cases and 1.3 million deaths attributable to TB. The TB mortality rate (MR) worldwide was 16.2 per 100 000 inhabitants [4]. In Europe, this MR drops to 2.3 per 100 000 inhabitants according to data from the European Centre for Disease Prevention and Control (ECDC) [5], while in Spain, according to the National Epidemiological Surveillance Network data (RENAVE in Spanish), the MR in 2022 was 0.4 per 100 000 inhabitants [6].

In 2014, the World Health Assembly adopted the "End TB" strategy, which aims to end the global TB epidemic as part of the United Nations (UN) Sustainable Development Goals. It serves as a blueprint for countries to reduce TB deaths and new cases by 95% and 90%, respectively, between 2015 and 2035, and to prevent any family from having to face catastrophic costs due to TB [7]. In line with this strategy, the Inter-Territorial Council of the National Health System in Spain launched the "National Plan for the Prevention and Control of TB" [8] in 2019, which aims to stop the transmission of TB in Spain through universal access to prevention, diagnosis and treatment.

There are different potential sources of information for TB mortality in Spain. The Spanish Surveillance System (SiViEs) is the official epidemiological surveillance database and collects the notifications of cases of TB from the different autonomous regions (Comunidades Autónomas in Spanish (CCAA)) through RENAVE. This epidemiological information is shared on an annual basis with the ECDC through the European Surveillance System (TESSy). There are other alternative sources from which we can obtain information on TB deaths, such as the National Statistics Institute (INE), which collects mortality from all causes through death certificates, or the minimum basic data set (CMBD), which collects data on TB through hospital discharge.

This study aimed to describe the TB mortality and related factors from 2008 to 2021 in Spain and to compare TB MRs across data sources (RENAVE, INE and CMBD) and with reported MRs across other EU/EEA countries.

Material and methods

We conducted a retrospective study comparing estimates of TB mortality in Spain from three data sources (RENAVE, INE and CMBD) between 1 January 2008 and 31 December 2021.

Sources of information

RENAVE

In Spain, pulmonary TB has been a mandatory notifiable disease since the beginning of the 20th century. However, until 1995, it was only compulsory to notify the total number of cases of pulmonary TB at the state level [9]. In 1995, RENAVE was created and a case-based TB notification and epidemiological survey of cases was established [10]. The regional surveillance systems individually report data on suspected, probable and confirmed cases of TB to the RENAVE through SiViEs, the technological platform that integrates all epidemiological surveillance processes [11].

Notification is carried out in accordance with guidelines and protocols agreed upon by the RENAVE members (the CCAA, Instituto de Salud Carlos III and Ministry of Health) [12]. Case definitions in TB protocol are based on the EU case definitions as published in the Official Journal of the European Union (Commission Implementing Decision (EU) 2018/945) [13] and on the Spanish Tuberculosis Surveillance Protocol [12].

Information collected from SiViEs included CCAA, province and municipality of residence, date of birth, sex, age, date of diagnosis, type of TB (pulmonary/extrapulmonary), HIV status, treatment outcome (completed/discontinued/cured/failed/lost/transferred/death or death for other cause) and death (yes/no). For the study of mortality and case fatality, since information on case fatal outcome is provided in RENAVE with two different variables – outcome variable (death from TB or death from other causes during TB treatment, among other outcomes and missing information) and variable death (Yes/No/missing value) – we built a new variable based on the WHO definition: death as a TB case dying from any cause before starting or during TB treatment. Thus, both the treatment outcome variable and the death variable were analysed, and a new variable was created by grouping cases where the death was "yes" and/or treatment outcome was death from TB or death from other causes during TB treatment [6].

INE

The official death statistics include information gathered at national, CCAA, provincial and municipal levels on the deaths that occur in Spain each year based on medical death certificates. This document is completed by the doctor together with the civil registry where the death is registered by the declarant or relatives [14]. Information collected from INE included CCAA, province and age from people whose main cause of death was TB and information on the official resident population of Spain, obtained *via* census.

Registry of Specialised Health Activity (RAE-CMBD)

The CMBD is a clinical-administrative dataset of hospitalisations that collects socio-demographic, clinical and administrative data from the National Health Service (NHS) discharge reports. In 2016, the CMBD was extended and renamed the Registry of Specialised Health Activity (RAE-CMBD) as a new model that included any contact established with the Spanish specialized healthcare network. All CMBD hospital notifications with TB placed as first diagnosis and type of discharge "exitus" between 2008 and 2021 were included. As these years include the transition from the CMBD to RAE-CMBD, it was necessary to export, homogenise and unify information from both datasets. Sociodemographic and administrative data (sex, age, date of admission and type of discharge) [15] were collected for each hospitalisation. This information was taken from the Statistical Portal of the Ministry of Health [16].

TESSy

Among countries in the EU/EEA, TESSy is the epidemiological surveillance system run by the ECDC, which collects data on incidence, mortality, treatment, multidrug resistance and estimated burden of TB disease. ECDC's annual surveillance reports are mainly intended for public health professionals and policymakers involved in disease prevention and control programmes. These reports are based on data retrieved from TESSy, a system for the collection, analysis and dissemination of data on communicable diseases. EU Member States and EEA countries contribute to the system by uploading their infectious disease surveillance data [17].

Annual MR estimates were extracted from these annual reports for 24 countries, those which had data available for the whole study period (Austria, Belgium, Croatia, Czechia, Denmark, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, UK and Switzerland). Data were collected from 2010 to 2021 [4, 5].

Data analysis

Cases of TB deaths collected by RENAVE, INE and CMBD were analysed. Cases with incomplete or unknown information (mainly year of death) were excluded from the analysis. A descriptive analysis was performed on the variables relevant to this study, including age, sex and year of death for the three databases, and HIV status and TB main location for RENAVE data.

Mortality rates

TB MRs per 100 000 inhabitants were calculated using official resident population information from the census as the denominator. MRs were computed across the study period and by year, sex and 10-year age groups for the three databases. The linear trends over the whole study period were also calculated.

Fatality and related factors

TB fatality rates were calculated according to RENAVE data for the whole period and according to TB location and HIV status. The relative risk of dying from TB among HIV and non-HIV patients during the study period was calculated by dividing the percentage of deaths in HIV-positive patients by the percentage of deaths in non-HIV patients.

Temporal evolution

Finally, time trends were calculated using Jointpoint regression analysis (Jointpoint software version 4.9.1.0; National Cancer Institute, Bethesda, MD, USA) [18] for the three databases. This analysis calculates annual mean percentage changes (AMPC) for annual MRs.

The software Stata version 18 was used for descriptive analysis. To show spatial patterns, we used GeoDa (2022) a software that helps in exploring and modelling spatial patterns.

TB mortality at EU/EEA level

For comparative purposes, MRs were computed for the data extracted from the ECDC reports. AMPCs were also calculated for countries for which MRs were available, and Spain's mean MR and AMPC were compared with the rest of EU/EEA.

Results

Between 2008 and 2021, 76 412 TB cases were reported to RENAVE, of which 47 532 (62.2%) were male. Of the total number of cases, information on treatment result was available for 79.8% (n=60 989), and there were 4127 (6.8%) deaths. For the same period, 3877 and 4775 TB deaths were reported to INE and CMBD, respectively.

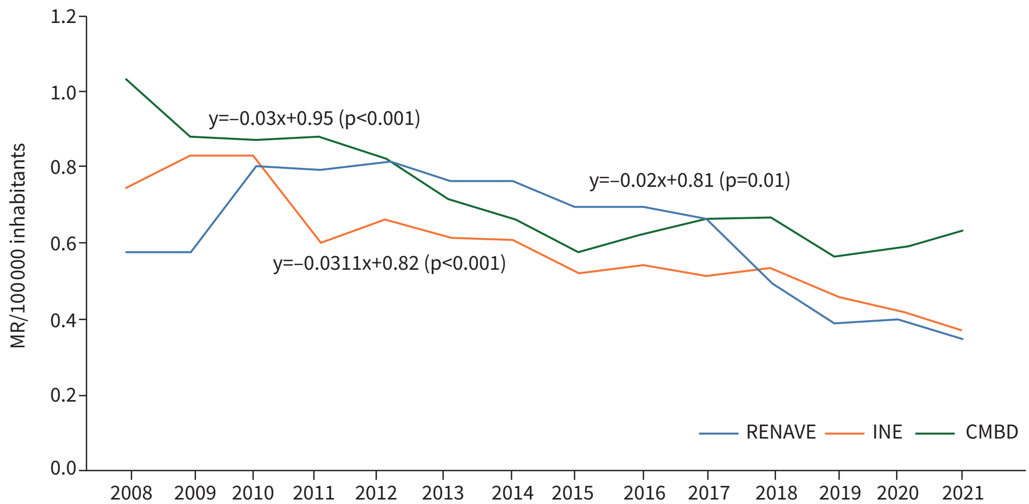

FIGURE 1 Evolution of tuberculosis mortality rates (MRs) from the National Epidemiological Surveillance Network (RENAVE), the National Statistics Institute (INE) and the minimum basic data set (CMBD). Spain 2008–2021.

Mortality rates

Across the study period, the MR was 0.62/100 000 (95% confidence interval (CI) 0.54–0.70), 0.59/100.000 (95% CI 0.52–0.66) and 0.72/100 000 (95% CI 0.65–0.79) inhabitants according to RENAVE, INE and CMBD, respectively.

The evolution of the MR rates across the study periods and their linear trends are different according to the data source. A statistically significant downward trend was observed in the three databases ($p<0.05$), although with different magnitude (figure 1).

Higher MRs were observed for men as compared to women across each of the three data sources and years. This difference between sexes remained stable throughout the study period, although the gap between men and women has narrowed throughout the study period in all three databases (figure 2). Differences were also observed by age group, with the highest MR in the three databases corresponding to the >80 years age group, where the highest differences in MR between sources were also observed (5.16/100 000 inhabitants in INE *versus* 4.0/100 000 inhabitants and 4.20/100 000 inhabitants in RENAVE and CMBD, respectively). The MRs from RENAVE and CMBD were higher than those from INE in the age groups up to 70–79 years. From this age onwards, the MRs calculated with the INE data were highest (see supplementary table S1).

Fatality and related factors

According to RENAVE data, although the main TB location was pulmonary (70.8% from all reported cases, n=54 101), the case fatality rate (CFR) across the study period was higher for meningeal and other

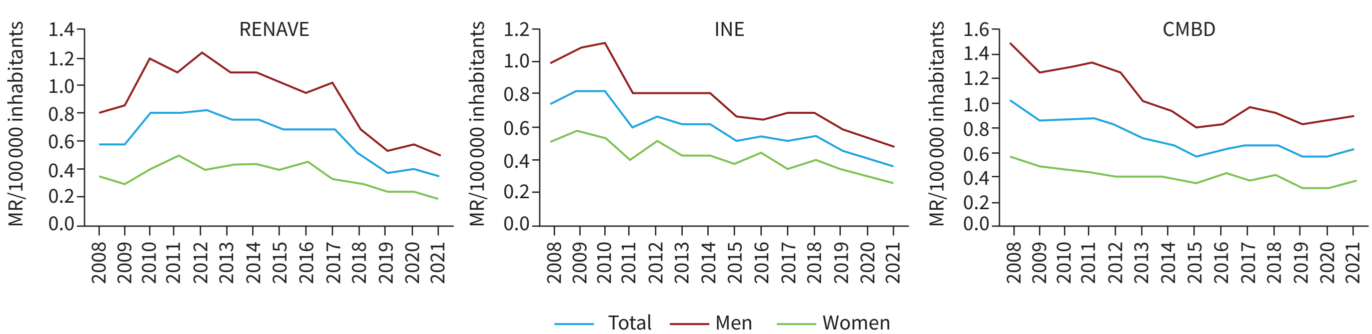

FIGURE 2 Evolution of tuberculosis mortality rates (MRs), total and by sex, from the National Epidemiological Surveillance Network (RENAVE), the National Statistics Institute (INE) and the minimum basic data set (CMBD). Spain 2008–2021.

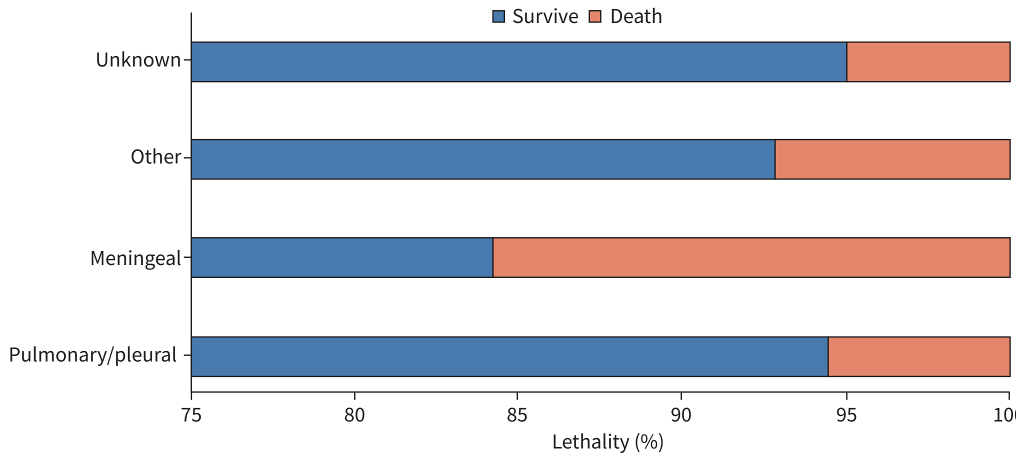

FIGURE 3 Percentage of deaths according to tuberculosis location.

TB sites. During the study period, 3191 deaths from pulmonary or pleural TB (CFR 5.5%), 155 deaths from meningeal TB (CFR 15.8%) and 1028 deaths from other TB (digestive, osteoarticular, genitourinary, *etc.* CFR 5%) were reported (figure 3).

On the other hand, HIV status was recorded for 60.3% of patients (n=46 053); of these, mortality data were available in 46 053 (78.1%). MR was higher for HIV patients in all study years except 2018, with a risk ratio for mortality calculated to be 2.02 (95% CI 1.82–2.2; p<0.05).

Temporal evolution

For the analysis of the mortality trend, the AMPC was computed. The highest AMPC was observed according to the INE (AMPC −5.22) followed by RENAVE (−4.61) and CMBD (−4.38).

TB mortality at EU/EEA level

Regarding MR at EU/EEA level, the countries with the highest MRs over 2010–2021 were Portugal (2.1/100 000 inhabitants), Poland (1.5), Croatia (1.2) and Hungary (0.9). Spain (0.6) ranked 8th among the 10 countries with the highest rates. Figure 4 shows the mean MRs in Europe for this period.

Regarding the temporal evolution, a downward trend was evident across all European nations except for Slovenia (with a positive AMPC of 1.20) and Luxembourg (3.37). A large heterogeneity throughout the territory was identified, ranging from a mean annual decrease of 11.3% in Hungary, 9.5% in the Netherlands or 9.3% in Sweden to an annual increase of 3.4% in Luxembourg or 1.20% in Slovenia. In Spain, an annual mean decline of 4.0% was observed. Figure 5 illustrates the AMPC observed in European countries across the study period.

Discussion

Through this study a picture of TB mortality in Spain according to different data sources is presented. A comparison with EU/EEA TB MRs is also shown.

We observed a downward trend in TB MRs in Spain over the study period, across all RENAVE, INE and CMBD data (with a statistically significant decline in all cases). This could be explained by improvements in TB diagnosis, prevention and treatment and also in living conditions, which have led to a significant reduction in TB deaths. This has been seen in other studies reporting a decline in TB deaths worldwide [4, 19]. However, the WHO has set a milestone of a 95% reduction in TB mortality by 2035, based on 2015 data. Achieving this goal would require a mean annual reduction of 9.5%, which is higher than the annual reductions of 5.22%, 4.61% and 4.38% achieved during the study period, according to INE, RENAVE and CMBD, respectively. It is therefore necessary to continue to improve the prevention and control of this disease in Spain.

According to our results, there is a higher number of TB-related deaths according to RENAVE data than according to INE data. This difference was already highlighted by Pedraz *et al.* [10] in describing the

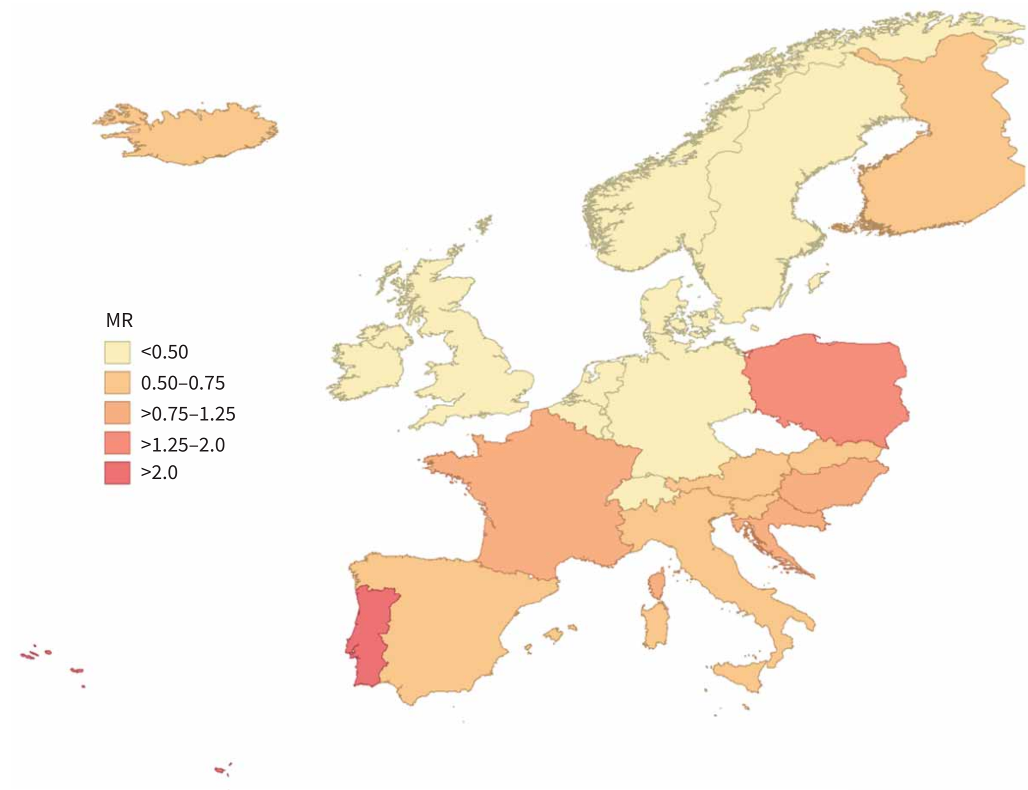

FIGURE 4 Mortality rate (MR)/100 000 inhabitants from 2010 to 2021, Europe, European Centre for Disease Prevention and Control (ECDC) data. Compilation based on TESSy database.

epidemiological situation of TB in Spain between 2012 and 2020. This could be explained by inaccuracy of death certificates, since errors in certification are common and range from incomplete certificates and illegible handwriting (or use of abbreviations) to inaccurate causes and manners of death [20]. On the other hand, the CMBD is the data source reporting the highest MR until 2012 and since 2017. This may be because CMBD data are taken from hospital discharges resulting in death, which are the most severe cases and therefore the most likely to die. However, as the main purpose of the CMBD is not to collect information on TB mortality, this should be interpreted with caution.

In all databases, TB mortality was higher in men than in women. Incidence of TB is also higher in men than in women, which could explain this difference [10]. These sex disparities have been extensively documented [21, 22] and could be due to factors such as higher rates of (re)infection or higher risk of severe TB among males (due to different exposure to risk factors or later diagnosis, and to increased male susceptibility associated with smaller B-cell follicles in the lungs) [23, 24]. However, the gap between men and women has narrowed in recent years. This may be due to improved access to healthcare for men in recent years, together with better adherence to treatment and/or improvements in clinical management of comorbidities (*e.g.* HIV-TB infection), which have traditionally led to a poorer prognosis for men with TB [25].

In our study, individuals aged over 70 years were the age group with highest MRs, which is consistent with other studies showing that older patients are most vulnerable to a fatal TB outcome [26]. Among other factors, this may be due to immunosenescence and frailty associated with older patients, as well as the higher prevalence of chronic diseases and comorbidities in these age groups [27].

According to RENAVE data, TB mortality varied according to the site of disease. Our data showed that even if the incidence of pulmonary TB was higher, the extrapulmonary CFR, especially in meningeal forms was higher. Several other studies have reported more deaths in extrapulmonary sites [28]. According to Rolo *et al*. [29], EPTB is more common in women, those at the extremes of age (<15 and >65 years), migrants, patients with HIV or those with immunosuppression. This may also contribute to the differences

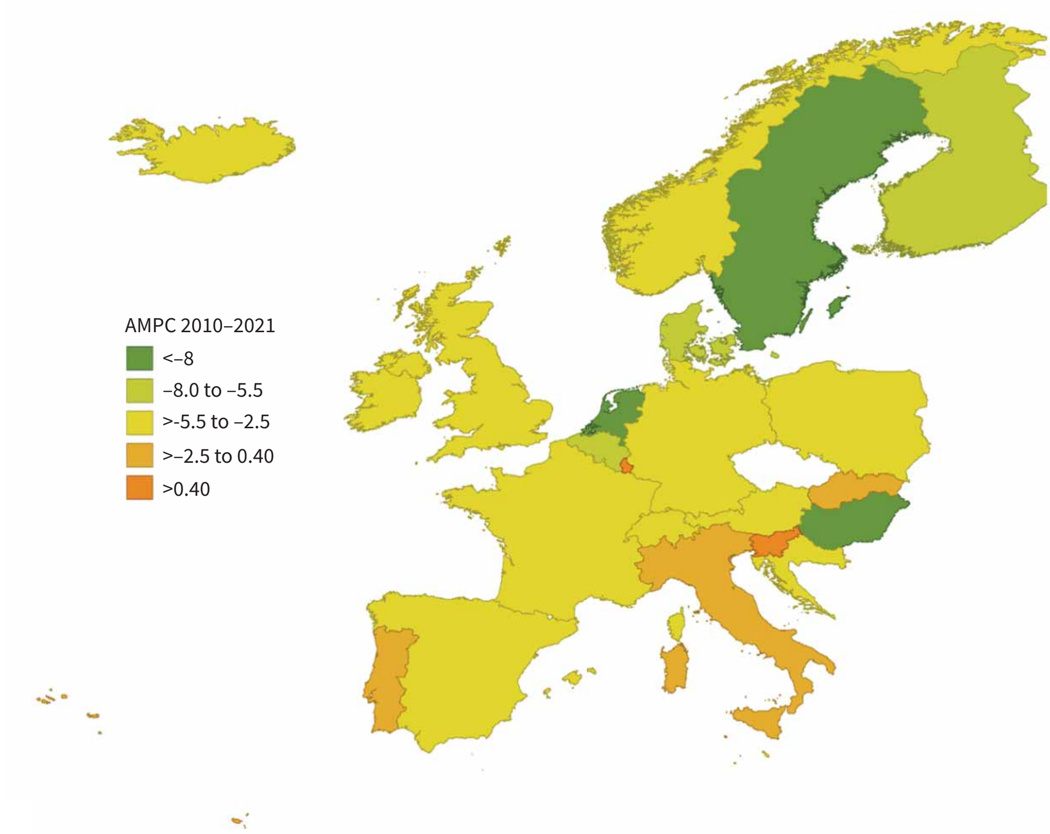

FIGURE 5 Annual mean percentage changes (AMPC) from 2010 to 2021, Europe. Compilation based on European Centre for Disease Prevention and Control (ECDC) data.

in TB mortality between age groups and patients with HIV in our study. In fact, TB is one of the leading causes of death in people with HIV [25]. We have seen that patients with HIV were two times more likely to die than patients without HIV according to surveillance data. This is consistent with the literature, which states that HIV co-infection is the strongest known risk factor for progression of TB infection to active disease and that it significantly increases TB-related mortality [30]. In fact, since 2004, WHO has recommended a collaborative HIV/TB package of activities consisting of integrating service delivery, reducing the TB burden through early antiretroviral initiation, and reducing the HIV burden in patients with presumed and diagnosed TB [31].

Spain ranked 8th among the 10 EU/EEA countries with the highest TB MRs. Differences in MR across Europe could be explained by several factors, such as BCG vaccination, incidence of multidrug-resistant TB, drug storage, data quality and incidence of HIV, work-related risk factors or social determinants.

The countries with the highest MRs were Portugal (2.1), Poland (1.5), Croatia (1.2) and Hungary (0.9). According to the ECDC [5], the prevalence of co-infection with HIV-TB varied and was highest in Portugal and Iceland (15%), which may explain some of these differences. The availability of first-line drugs to TB is also uneven across European countries. A study of the availability of these drugs across Europe found that only 13 (43.3%) of the countries surveyed had all four first-line anti-TB drugs available for adults [32].

Another important factor is immigration, as the proportion of TB cases among migrants has increased, and a cross-sectional secondary database analysis showed that among migrant TB cases, 45.2% were extrapulmonary compared with 21.7% among non-migrants ($p<0.001$). This could also explain the increase in mortality in countries with higher immigration rates [33]. Migrant TB patients accounted for 33% of all reported TB cases in EU/EEA countries in 2021 [5], which could also mean that cases are concentrated in more vulnerable populations with greater difficulties in adherence and access to treatment, which in turn could lead to an increase in mortality. Finally, another factor that could explain differences is drug-resistant TB, which is a major global health risk that increases the morbidity and mortality of TB worldwide [34].

Limitations

In the CMBD and INE, by considering only the main diagnosis, information was lost on the cases with TB diagnosis as secondary cause. Moreover, the completeness of some variables was low in RENAVE. In the last available RENAVE report from 2022 [6], the serological HIV status was missing in 35% of the cases. Also, this information bias could be influenced by the type of TB: pulmonary forms, which have been notifiable for a longer time, and require more follow-up due to the study of contacts, might be more exhaustively reported. As we were unable to compare the databases at the individual level to estimate the overlap between them, we cannot calculate the real number of TB deaths during the study period.

Furthermore, this is a descriptive analysis that does not allow for associations between variables and therefore does not allow for comparison of risk factors, which were also only available from one source. Further studies should be carried out to extend the information and provide high-quality data for more robust comparisons.

Despite these limitations, the joint analysis of each of these databases increases knowledge of TB mortality in Spain. The CMBD is not designed as a surveillance system, but its information may improve the completeness of the registries, as it has already been proven with other diseases [35, 36].

Conclusions

Tuberculosis is a very important public health disease. For this reason, the WHO "End TB strategy" aims to reduce by 90% deaths from TB by 2030 compared to 2015. Although the TB MR in Spain has followed a downward trend over the period studied, to achieve this target, we would need to maintain a mean annual reduction of 9.5%, which is higher than the mean decline achieved for the 2008–2021 period (4%). Therefore, it is necessary to continue to improve the prevention, diagnosis and treatment of TB, especially in the most vulnerable groups, such as men and people over 75–80 years of age. In addition, comprehensive measurements are needed to account for improvements, so more knowledge and better use of all information systems are needed to complement monitoring systems, to compensate for registries' limitations, in order to fill information gaps and to implement strategies using resources in the most efficient way.

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