

Tuberculosis Epidemiology in Area 15 of the Spanish Autonomous Community of Valencia: Evolution From 1987 Through 2001

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OBJECTIVES: To describe the evolution of tuberculosis epidemiology in Area 15 of the Autonomous Community of Valencia.

MATERIAL AND METHODS: Cases of tuberculosis were identified by active case finding in Area 15 from January 1987 through December 2001. Clinical and epidemiological data were extracted from case records and a patient interview.

RESULTS: Four hundred seventy-six diagnosed cases of mycobacterial infection were identified (459 tuberculosis, 16 atypical, and 1 mixed); 423 tuberculosis patients were residents of Area 15. The mean annual incidence rate was 24.6/100 000 population, representing a rate decrease of 41.5% from 1990. The most frequent risk factors were smoking (38%), alcoholism (20%), human immunodeficiency virus (HIV) infection (18%), and contact with a tuberculosis patient (14%). The site of tuberculosis involvement was the lung in 61% (49% bacillus positive, with a nonsignificant trend to decrease over time), nonpulmonary in 26%, and mixed in 13%. The radiographic pattern observed most often was pulmonary infiltrates (67%), and lower lobe involvement tended to increase over time. Diagnosis was by acid-fast bacillus stain for 77%, clinical picture for 16%, and histological for 7%. Isoniazid resistance was detected in 1.5% and rifampicin resistance in 0.3%. Patients were hospitalized during diagnosis in 79% of cases; the mean stay was 18 days.

CONCLUSIONS: The incidence of tuberculosis has decreased in spite of the HIV pandemic. Risk factors have not changed, bacteriological diagnosis has improved, and the location of pulmonary infiltrates has changed. No influence of immigration on the incidence rate of tuberculosis has been detected to date.

Key words: Tuberculosis. Epidemiology. Human immunodeficiency virus (HIV). Evolution.

Evolución de las características epidemiológicas de la tuberculosis en el Área 15 de la Comunidad Valenciana en el período 1987-2001

OBJETIVOS: Valorar la evolución de las características epidemiológicas de la enfermedad tuberculosa (TB) en el Área 15 de la Comunidad Valenciana.

MATERIAL Y MÉTODOS: Mediante búsqueda activa se identificaron todos los casos de TB diagnosticados en el área desde enero de 1987 a diciembre de 2001. Se recogió información clínica y epidemiológica de la historia clínica y de la entrevista con el paciente.

RESULTADOS: Se diagnosticaron 476 casos de micobacteriosis (459 TB, 16 atípicas y una mixta), de los cuales eran residentes en el área 423 casos de TB. La tasa media anual fue de 24,6/10⁵, con un descenso del 41,5% desde 1990. Los factores de riesgo más frecuentes fueron: tabaquismo en el 38%, etilismo en el 20%, infección por el virus de la inmunodeficiencia humana (VIH) en el 18% y contacto con TB en el 14%. La localización fue sólo pulmonar en el 61% de los casos (bacilíferos en el 49%, con tendencia a disminuir, aunque no significativamente), extrapulmonar en el 26% y mixta en el 13%; los infiltrados (67%) constituyeron el patrón más frecuente, con tendencia al aumento de incidencia en los lóbulos inferiores. El diagnóstico fue bacteriológico en el 77% de los pacientes, clínico en el 16% e histológico en el 7%. Fueron resistentes a isoniácida el 1,5% de los casos y a rifampicina el 0,3%. El 79% ingresó para diagnóstico, con una estancia media de 18 días.

CONCLUSIONES: La TB ha disminuido su tasa, pese a la pandemia del VIH. No hay cambios en los factores de riesgo, se ha mejorado el diagnóstico bacteriológico y hemos observado cambios en la localización de los infiltrados pulmonares. La inmigración no ha tenido por el momento influencia sobre la tasa de TB.

Palabras clave: Tuberculosis. Epidemiología. Virus de la inmunodeficiencia humana (VIH). Evolución.

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Introduction

Following years of sustained decline in the number of cases of tuberculosis in industrialized countries, increased incidences were detected coinciding with the human immunodeficiency virus (HIV) pandemic. The

tuberculosis situation in Spain has been worrying for many decades owing to inadequate public health policies, leaving this country at the tail end of developed countries with respect to tuberculosis control. Thus, Spain had the second highest national incidence among European countries in 1995.¹ Although epidemiological information for all of Spain is limited and there are differences in the definitions of cases for which reporting is mandated, the past 15 years have seen growing interest in improving the situation, as shown by studies coming from the Assembly on Tuberculosis and Respiratory Infections of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).²⁻⁵

The aim of the present study was to analyze changes in the rate of tuberculosis in Public Health Area 15 of the Autonomous Community of Valencia and to describe the epidemiological characteristics of change.

Material and Methods

Population

All cases of tuberculosis diagnosed in Public Health Area 15 of the Autonomous Community of Valencia between January 1987 and December 2001 were studied.

To calculate the population and population pyramid for the area, municipal census information was gathered for each of the studied years. This process indicated that the area had 96 101 legal residents in 1987 and 131 258 in 2000, corresponding to 2.8% of the entire population of the Autonomous Community of Valencia. Specialized health care was provided from a dedicated unit at a 300-bed general hospital (Hospital Marina Baixa) serving the area. Primary care was given from 6 health care clinics and 16 auxiliary clinics in the smallest villages. Area 15 also has a 100-bed private hospital that mainly serves foreign tourists. All samples for analysis were processed by the microbiology department of Hospital Marina Baixa.

Definition of Cases

For epidemiology, a tuberculosis case was defined as any patient for whom antituberculosis treatment was prescribed and who complied with the full course of treatment. If the patient died or experienced side effects that led to withdrawal of treatment, that patient was still considered a case. Patients who restarted treatment were admitted as new cases if more than a year had passed since treatment had been abandoned. Patients were classified as either sputum smear positive or negative. Patients in whose samples nontuberculous mycobacteria were isolated were classified as not having tuberculosis.

Data Collection

Information about tuberculosis was gathered by reviewing hospital admissions records, by records of positive Ziehl-Neelsen and/or Löwenstein stains reported by the microbiology department, by findings reported by the pathology department, and by the registry of patients with diseases subject to mandatory reporting. We also gathered information about cases reported personally by colleagues at the hospital and the primary health care clinic. Once a

tuberculosis case was identified, patient characteristics and sociodemographic, clinical, and microbiological variables were obtained by reviewing patient records or by some other means. Data were stored in a computer database for later statistical analysis.

The number of HIV infections each year was obtained by first adding the number of patients from the previous year to those newly diagnosed by the central laboratory (where all such diagnoses for Area 15 were made) in the next year, plus patients treated at the day hospital who had been diagnosed in other public health areas but who lived in Area 15.

Strains were sent to the Spanish national reference laboratory for mycobacteria (National Center of Microbiology in Majadahonda, Madrid) for identification. There, the proportions method of Canetti, Rist, and Grosset was used to study the sensitivity of the strain to the following antimicrobial agents: isoniazid, streptomycin, ethambutol, rifampicin, and pyrazinamide.

Epidemiological Analysis

The Rsigma software program (Horus, Madrid, Spain) and EpiInfo 6.1 were used to study:

1. Annual incidence rates, distribution by age groups, sex, and residence. The mean annual incidence rate and the annual incidence rates for the study period, calculated in accordance with updated municipal census records, were used. The Student *t* test was applied to compare means and either a χ^2 or Fisher exact test was applied, as necessary, to compare proportions, taking a 95% confidence interval (CI) with the level of statistical significance set at $P < .05$. For analysis by age groups, we applied the categories suggested by the Assembly on Tuberculosis and Respiratory Infections of SEPAR.⁵ Only tuberculosis cases resident in Area 15 were included in the calculations (cases diagnosed in nonresidents were excluded).

2. Association between tuberculosis and the variable sex. To evaluate the association between variables, we calculated relative risk (RR) with a 95% CI.

3. Trends by epidemiological characteristics and rates. Trends were calculated by linear regression or by the Mantel-Haenszel test. Statistical significance was set at $P < .05$. Annual decline was calculated based on the mean for each year.

Results

During the 15 years covered by this study, 476 cases of mycobacterial infection (459 tuberculosis and 16 due to environmental mycobacteria, and 1 concomitant infection by environmental mycobacteria and *Mycobacterium tuberculosis* in an HIV-positive patient). Thirteen (76%) of the cases with environmental mycobacterial infection occurred in patients who were HIV positive and 4 occurred in HIV-negative patients. Of the 460 tuberculosis cases, 37 were nonresidents and 423 were residents of Area 15, giving a mean annual incidence rate of 24.6 per 100 000 population after nonresidents were excluded. The mean annual decline was 3.8% for the general population and 9.1% for children under 15 years of age (Figure 1). Changes over

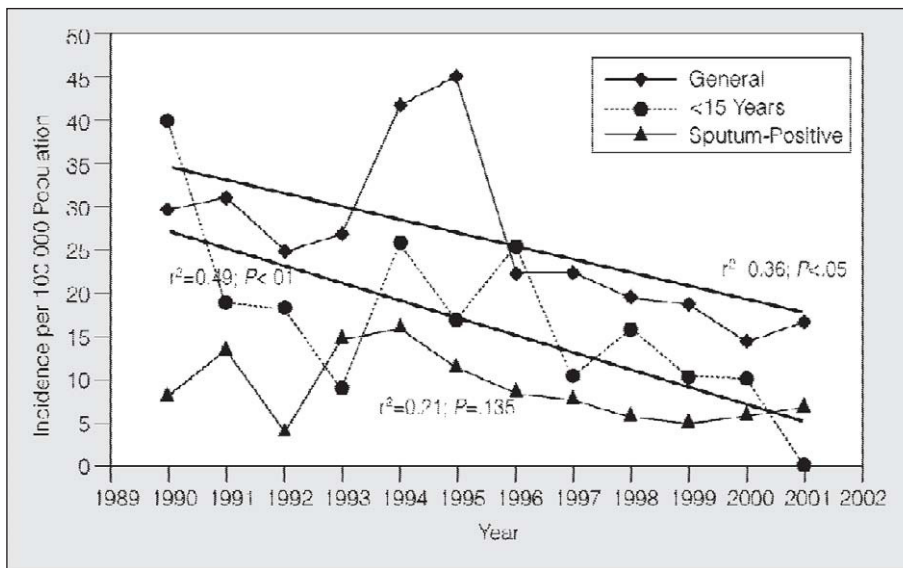


Figure 1. Changes in rates of tuberculosis in Public Health Area 15 of the Autonomous Community of Valencia, 1990 through 2001.

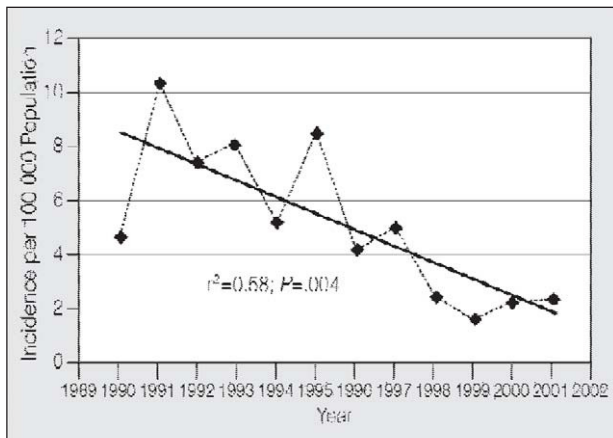


Figure 2. Changes in the rate of coinfection by tuberculosis and human immunodeficiency virus in Public Health Area 15 of the Autonomous Community of Valencia, 1990 through 2001.

TABLE 1
Number of Tuberculosis Cases and Incidence per 100 000 Population, and Trends From 1990 through 2001: Totals by Age Groups and Sex

Patient Characteristics	Number of Cases (Incidence)		Mean Incidence	Changes in Number of Cases (Changes in Incidence)
	1990	2001		
Age, years				
0-4	2 (27)	0 (0)	19.55	-2 (-100%)
5-9	3 (33.7)	0 (0)	14.64	-3 (-100%)
10-14	5 (56.6)	0 (0)	16.32	-5 (-100%)
15-24	4 (24.2)	4 (21.2)	23.61	0 (-12.4%)
25-34	4 (24.6)	5 (24.2)	36.18	+1 (-1.6%)
35-44	4 (29.5)	4 (20.5)	36.9	0 (-47.8%)
45-54	4 (35.4)	3 (18.6)	27.3	-1 (-47.5%)
55-64	1 (8.7)	4 (29.9)	21.03	+3 (+243.7%)
>64	5 (38.1)	3 (13.3)	19.31	-2 (-65.1%)
Sex				
Male	17 (31.9)	17 (26.3)	26.7	0 (-17.56%)
Female	15 (27.7)	6 (9)	18	-9 (-67.5%)
Total	32 (29.8)	23 (17.52)	25.8	-9 (-41.5%)

time for other age groups are shown in Table 1. Of patients with pulmonary disease, 49% gave sputum specimens that proved positive, for a mean incidence of 9 per 100 000 population with a nonsignificant tendency to decrease ($r=-0.46$; $P=.135$) (Figure 1). Only 4 tuberculosis cases were found in immigrants, although all of them had been diagnosed within the past 2 years.

Active case finding carried out systematically by the respiratory medicine service and the public health authorities of Area 15 led to a change in mean incidence from 14.7 per 100 000 population, which would correspond to the 253 cases registered as a result of the mandated reporting program in effect, to a rate of 24.6 per 100 000 population, which would reflect the 423 cases we found. Reporting improved over the course of the study ($r=0.79$; $P<.0001$).

Twenty-two patients (5.2%) died while ill, a rate of 1.3 per 100 000 population; 12 of those deaths were due to a concomitant illness and 10 were due to tuberculosis, making the mortality rate due to tuberculosis 0.6 per 100 000 population. Of those who died, 45% were over 65 years of age and 75% of those who were younger were HIV coinfecting. No differences were found between sexes.

Seventy-three cases (16%) were HIV coinfecting, representing a mean annual incidence of 3834 per 100 000 coinfecting individuals, an evident decrease since initiation of highly active antiretroviral treatments. Changes in the tuberculosis incidence rate in the HIV-coinfecting population can be seen in Figure 2. The mean age for this subsample was 35 years (range, 5-61 years) whereas the mean age of the 350 HIV-negative cases was 38 years (range, 1-87 years; $P<.01$).

Distribution by sex showed that 278 patients were males and 145 were females, indicating an incidence rate of 32.8 per 100 000 for males and 16.6 per 100 000 for females and a 2:1 ratio of males to females. Higher incidence rates among males were seen throughout the

TABLE 2
Number of Tuberculosis Cases and Incidence, 1990 Through 2001. Distribution by Municipalities

Municipalities	Incidence Rate per 100 000 Population		Mean Incidence	Changes in Incidence (%)
	1990	2001		
>5000 inhabitants				
Alfaz del Pi	12.30	7.07	11.31	-42.52
Altea	15.57	6.42	13.82	-58.77
Benidorm	55.34	22.1	38.7	-60.10
Callosa d'Ensarria	12.58	30.8	10.38	+144.80
La Nucia	16.86	0	12.96	-16.86
Villajoyosa	12.75	21.1	20.6	+65.50
<2500 inhabitants				
All municipalities	13.42	23.78	25.08	+77.20
Whole area	29.8	17.5	25.8	-41.5

study period (RR=1.97; 95% CI, 1.61-2.41; $P<.0001$). Two moments of peak incidence were observed: in 1991 and from 1994 to 1995. The latter was much higher and both occurred mainly in males. The distribution by age groups and by sex for all age groups is shown in Figure 3. Changes between January 1990 and December 2001 can be observed in Table 1.

The incidence of tuberculosis in different towns and changes between 1990 and 2001 are presented in Table 2.

The most common predisposing factors were smoking (38%), alcoholism (20%), HIV infection (18%), contact (14%), and intravenous drug addiction (12%). One predisposing factor was identified in 149 cases (35%), 2 in 103 (24%), 3 in 40 (10%), and 4 in 4 (1%). No predisposing factor was found in 119 cases (28%). The distribution of risk factors for the total population and the HIV-negative and HIV-positive

TABLE 3
Distribution of Risk Factors*

	Total Population (n=423)	HIV-Negative Population (n=350)	HIV-Positive Population (n=73)	P
Risk factor				
Gastrectomy	6	6	0	NS
Alcoholism	81	68	13	NS
Diabetes	18	17	1	NS
Hemodialysis	1	1	0	NS
Corticosteroids	9	9	0	NS
Chemotherapy	2	2	0	NS
Intravenous drug addiction	50	7	43	<.001
Smoking	159	129	30	NS
Neoplasm	18	15	3	NS
Silicosis	6	6	0	NS
CRF	3	3	0	NS
TB contact	57	56	1	<.001
Untreated TB	12	12	0	NS
Number of factors				
0	119	119	0	<.00001
1	149	136	13	<.001
2	103	69	34	<.001
3	40	16	24	<.001
4	4	1	3	<.05

*HIV indicates human immunodeficiency virus; CRF, chronic renal failure; TB, tuberculosis. NS, not significant.

populations, and the difference between the latter 2 subpopulations, can be seen in Table 3. The period studied saw a) a significant increase in infection among persons addicted to intravenous drugs between 1990 and 1998, when the rate went from 3% to 18%, after which it decreased to 2% in the 1999 to 2001 period, and b) a tendency toward decline in the number of patients without a known risk factor ($r=-0.52$; $P<.05$) or with a history of gastrectomy ($r=-0.64$; $P<.01$).

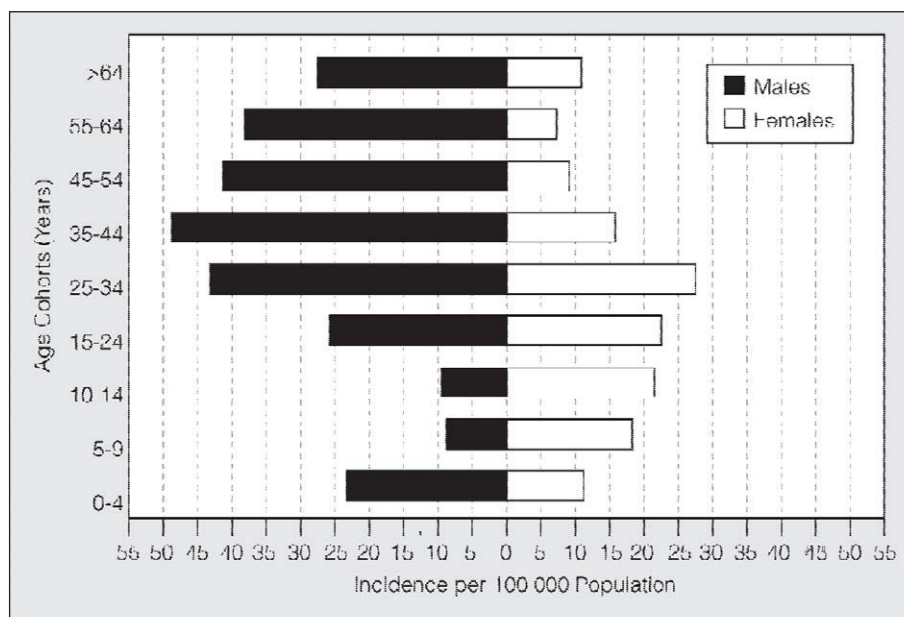


Figure 3. Mean annual incidence of tuberculosis in Public Health Area 15 of the Autonomous Community of Valencia from 1987 through 2001.

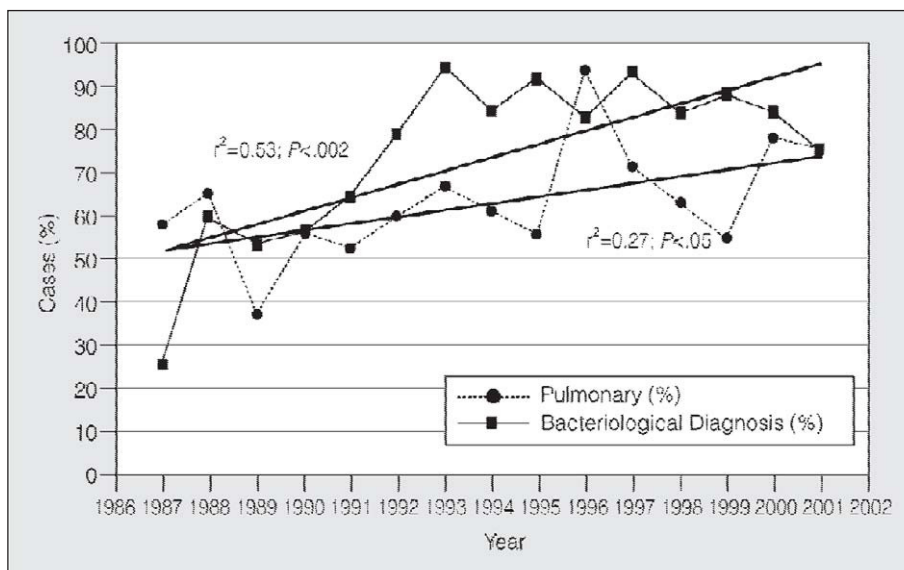


Figure 4. Trends in pulmonary tuberculosis and bacteriological diagnosis, 1987 through 2001.

Tuberculosis was confined to the lung in 259 (61%) cases, was mixed in 56 (13%), and was entirely nonpulmonary in 108 patients (26%). Over the course of the study, the proportion of cases confined to the lung tended to increase ($r=0.52$; $P<.05$). A nonsignificant trend for the rate of mixed or nonpulmonary infection to decrease was noted.

Among pulmonary tuberculosis cases, infiltrates were the most common radiographic pattern, seen in 207 (67%) cases. Cavitation was the second most common radiographic finding, with 91 (29%) cases, followed by 61 (20%) with miliary, nodular, or normal images. For cases with nonpulmonary thoracic involvement, pleural effusion with 67 cases (18%) and hilar lymph node and/or mediastinal involvement with 36 cases (10%) were the most frequent clinical pictures, in proportions unchanged over the course of the study. The most frequent locations of pulmonary infiltrates were the right and left upper lobes, for which the mean annual incidence rates were 42% and 26%, respectively. Those rates did not change significantly over the course of the study. Lower lobe localization tended to increase in frequency (χ^2 for trend, 6.71; $P<.01$). No information was available for 10 (3%) cases.

Diagnosis was clinical in 66 (16%) cases, bacteriological in 326 (77%), and histological in 31 (7%). Diagnosis was clinical in 40 (13%) of the 315 patients with pulmonary involvement and bacteriological in 267 (85%). Figure 4 shows trends in the number of cases with pulmonary involvement and with bacteriological diagnoses. A positive sputum smear was obtained for 49% of cases with pulmonary involvement, although only the culture was positive in 18%. Positive findings in bronchial aspirates and bronchoalveolar lavage fluid were obtained in 24 cases (7.6%). Of the 108 patients with tuberculosis confined to the lung, 59 (55%) had at least 1 positive culture of a sample. Over the course of the study a

decrease was seen only in the number of cases diagnosed clinically ($r=-0.76$; $P<.01$).

Of the 326 cultures of *M tuberculosis* for which sensitivity was studied, 5 (1.5%) had primary resistance to isoniazid and 1 (0.3%) to rifampicin.

Three hundred thirty-four patients (79%) were hospitalized for diagnosis. The mean length of hospital stay was 18 days, and the diagnosis was postmortem in 5 cases.

Discussion

The rate of tuberculosis infection in our public health area is similar to that of the rest of Spain³ and well below that of some public health areas or autonomous communities in Spain.⁶⁻¹² The age distribution, which reveals the peak incidence to be in young adults, is far from the profile expected for a country that has the disease well under control.^{13,14}

Tuberculosis declined in our area in a manner similar to the decline in the United States of America as a whole or in certain of that country's states^{14,15} and is less marked than the decline reported in other Spanish studies.^{5,12,16,17} Declines have not been reported for all European Union countries nor all areas of Spain, however.^{6,7,18} All but 2 age groups experienced a decline. Tuberculosis decreased most in those under the age of 15 years, an observation consistent with reports from other communities,^{12,17,18} probably due to the overall decrease in tuberculosis disease and the consequent reduction in annual risk of infection,¹⁸ which may be an indication that we are providing better treatment for our older patients. The highest incidence was found in young adults,^{16,19} influenced considerably by the HIV pandemic although as in other areas¹⁷ it did not affect the overall tendency toward decline.

The rate of sputum-positive cases was lower than that found in other Spanish studies, whether they were done

in large population groups or in specific public health areas,^{3,7-11,20} although it differs a great deal from the rates in other countries.^{13,14,21} Although the rate of sputum-positive cases declined over time, the changes were not significant. From Figure 1 we can infer that changes did not take place at a steady rate: a first period from 1990 to 1994 showed no change and a second period from 1994 to 2001 displayed a trend for the frequency of sputum-positive cases to decrease that can not be attributed to the decline in HIV infection, given that the decrease in tuberculosis in the HIV-positive population occurred with the application of highly active antiretroviral therapy in 1997.²²

The registry was notified of 60% of the diagnosed cases, a rate that points to continued improvement since 1999.²³ However, there continues to be considerable variation from one Spanish area to another.^{3,8,10,24}

The mortality rate for patients with tuberculosis found in our study is lower than that of Vizcaya or the Community of Madrid, for both deaths of patients with tuberculosis and deaths from tuberculosis,^{25,26} although the curve is bimodal. One peak reflected 9 deaths among patients aged 25 to 45 years old, 80% of whom were HIV coinfecting. The other peak, reflecting 10 deaths, occurred in patients over 65 years of age.

The rate of HIV coinfection seems similar to that reported in other cross-sectional⁹ and longitudinal studies,^{17,19,27} although the HIV status was unknown in 61% of the cases in the studies of Díez et al¹⁹ and the working group of the Multicenter Project for Tuberculosis Research.⁹ The rate of HIV coinfection varies greatly from area to area, ranging from 3.3% to 40%,^{6-8,10,11,16,28} the higher rate differing greatly from those reported for other countries. In our area, 13% of all tuberculosis cases are related to HIV infection, even though the introduction of highly active antiretroviral treatment improved the situation.

The observations for distribution by sex are consistent with those reported by other authors inside and outside Spain. Tuberculosis is approximately twice as common among males,^{6,9,10,19,25} but no trend was seen over the course of the study.

Risk factors found were mainly those reported in the literature.^{8,18,29,30} Because there are multiple risk factors for tuberculosis and no consistency in data collection, it is difficult to compare studies, although it is also true that risk is not the same from area to area.^{8-10,16,18,30,31} The only change related to risk observed was a tendency toward decline in the number of patients with no risk factor or with a history of gastrectomy, the latter finding probably owing to the decrease in application of that therapeutic approach.

The rates for location of infection were similar to others published for Spain^{8,9,19,30} and other European countries,¹⁸ although coinfection by HIV can lead to great variation,²⁸ with a tendency in our area for the rate of exclusively pulmonary disease to rise, possibly due to the gradual decrease in HIV coinfection. Patterns on chest radiographs were similar to those reported in the

literature^{8,32}: the most common pattern was pulmonary infiltrates, seen mainly in the upper lobes and on the right side, although that finding is not always present. Cases with miliary or nodular images or with normal radiographs were more numerous than expected, and the frequency of infiltrates found in the lingula and middle and lower lobes tended to rise—both findings certainly favored by HIV coinfection.

The percentage of pulmonary tuberculosis cases with positive sputum smears was similar to rates reported for some areas,¹⁹ but much lower than rates for others, especially for the Autonomous Community of Galicia.^{10,11} No trends were noted for sputum positivity in our area, in contrast with a decrease of 5.15% reported for Spain as a whole.³

A high percentage of patients were hospitalized for diagnosis, consistent with most reports in the literature,^{8,19,24} although health care areas with more experience with tuberculosis control programs tend have lower hospitalization rates.

The rate of bacteriological diagnosis of patients with lung involvement was high, as has been reported previously,^{8,13,19,27} and there was a tendency toward improvement over time. *M tuberculosis* strains that were resistant to first-line drugs were not found often. Resistance, however, varies greatly from one geographic area to another.^{15,18,19,21,28,35}

We conclude that the incidence of tuberculosis in our public health area decreased over the 15-year period studied, in spite of the HIV pandemic. Risk factors changed little. We managed to improve the rate of bacteriological diagnosis over time. Nevertheless, the hospitalization rate was high and should be reduced. Changes in the location of pulmonary infiltrates were observed, possibly as a result of the HIV pandemic, and immigration had not had an important effect on the rate of tuberculosis at the time the study ended.

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