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The decline of autochthonous leprosy in the Valencia Region of Spain: patterns and trends 1940–2015

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Summary

Objectives: The aim of this study was to describe the patterns and trends of autochthonous leprosy in the Valencia Region (Spain).

Methods: We included all new leprosy cases originating from the Valencia Region between the years 1940 and 2015. Patients originating from other countries or other Spanish regions were excluded. New cases were analysed by age, sex, clinical type, occupation, and geographic distribution.

Results: A total of 442 patients with presumably autochthonous leprosy were included. Incidence rates consistently declined over the study period. Mean age at onset gradually increased from 34.2 years during the period 1940–1949 to 59.5 years during 2000–2015. There were no cases with clinical onset after 2006 and no cases born after 1973. Patients were predominantly males (57.7%) and 85.4% had multibacillary leprosy. The proportion of multibacillary cases increased gradually

after 1970. The majority of male patients (67.9%) worked in agriculture. Most of the cases, especially during the later periods, were concentrated in the coastal regions. *Conclusions:* Our findings are consistent with trends described in other regions with declining leprosy incidence rates and suggest that the transmission of *M. leprae* infection in this area may well have now stopped. Autochthonous leprosy in this region has had a male predominance and a high proportion of multibacillary cases. The geographic distribution and the high incidence in agricultural workers suggest that environmental factors should be further explored.

Introduction

Leprosy has long been endemic in Spain, with four areas of high prevalence: the east coast (which includes the Mediterranean regions of Cataluña, Comunidad Valenciana [Valencia Region] and Murcia), Andalucía in the south, Galicia in the northwest, and the Canary Islands.¹ Throughout the 19th century, the highest prevalence was found in the east coast, but this was surpassed by Andalucía during the second half of the 20th century.^{1–2}

Although several leprosy hospitals had long existed in Spain for the isolation and treatment of patients, a national leprosy control programme did not start until the 1940's after the end of the Spanish civil war. This programme brought about the creation of new healthcare centres and mobile teams for contact tracing and active case finding, which led to an increase in case detection rates during the years 1940–1950.¹ Sulfones were introduced in 1945, and from 1981 short-course multiple drug therapy was consistently used. The case detection rates have been steadily declining since 1950 and during the last 10 years more than 70% of the new cases have been imported.^{3–9}

Observations in several countries with declining leprosy incidence rates have found consistent trends - including increasing age at onset (associated with delayed infection and an increasing proportion of patients with long incubation periods), and an increasing proportion of male cases and multibacillary (MB) forms.^{10–13} The latter trends have been explained by reference to evidence that males have a relative predilection for MB disease, and MB disease has a longer incubation period than paucibacillary (PB) disease.^{10,14} These trends have not yet been investigated in Spain.

The Valencia Region (Comunidad Valenciana), located in the east Mediterranean coast of Spain, is formed by three provinces (Castellón, Valencia, and Alicante, from north to south) (Figure 1) and has long been an endemic leprosy area.

The Fontilles leprosy hospital (Sanatorio de Fontilles) opened in Alicante in 1909 for the treatment and isolation of leprosy patients and is still functioning. Most of the patients from the Valencia Region were admitted (as inpatients or outpatients) at this hospital, as well as a few patients from other Spanish regions, and a complete registry of all patients has been kept. This provides a unique opportunity to investigate the patterns and trends of leprosy in this European region with declining incidence rates.

The aim of this study is to describe the patterns and trends of autochthonous leprosy in the Valencia Region between the years 1940 and 2015.

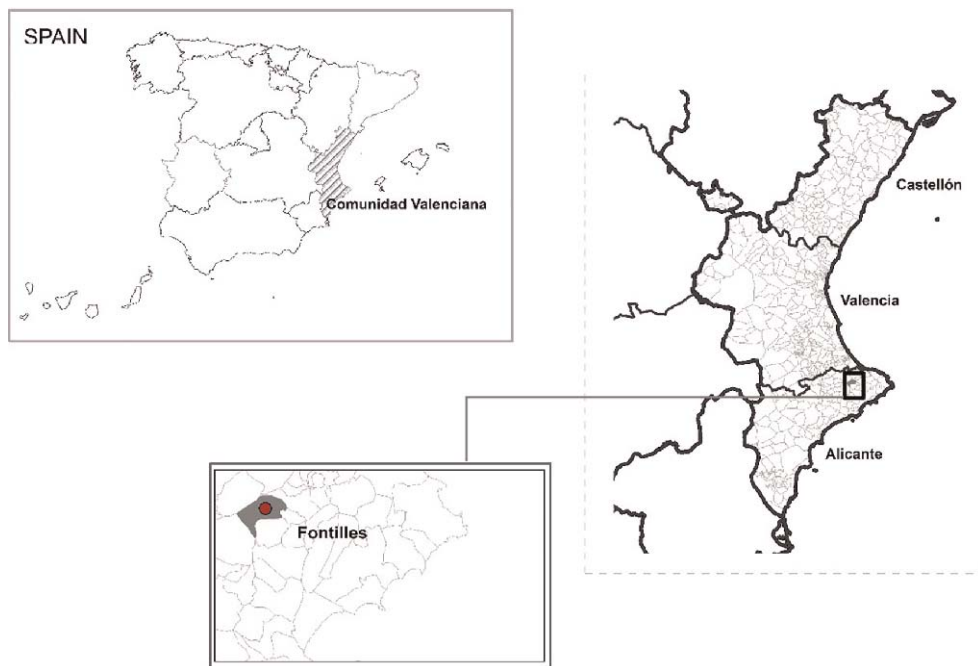


Figure 1. Location of the Valencia Region (Comunidad Valenciana) in Spain. The region's three provinces, the distribution of their municipalities, and the location of the Fontilles leprosy hospital, are also shown.

Materials and Methods

MATERIALS

The main source of data was the Fontilles registry, which includes all patients admitted as inpatients or outpatients from 1909 to 2015, from the Valencia Region or elsewhere. Completeness was only reliable from 1940, so only cases having clinical onset after this date were included. Additionally, as all cases of leprosy are required to be reported to the regional health authority, we reviewed records from the Valencia Region leprosy registry, which should include all patients diagnosed in this region from 1940 to 2015 in any health centre. All patients were reviewed in both registries to check for duplicate records or inconsistent patient descriptions, and corrected as needed.

Data on the following variables were extracted: birth date, date of clinical onset, age at clinical onset, date of admission (in Fontilles), sex, village of birth, village of residence, village of diagnosis (only available in the Valencia Region database), travels abroad before clinical onset (this variable was only available in the Fontilles registry), classification (multibacillary [MB]/paucibacillary [PB]), occupation (only available in Fontilles), disability grade at diagnosis (only available in the Valencia Region registry) according to WHO 1988 classification¹⁵ and family and non-family contacts with leprosy.

Population data for the Valencia Region, its three provinces and all their villages were extracted from the Spanish censuses provided by the National Statistics Institute.¹⁶

METHODS

The analysis was restricted to autochthonous cases (i.e. who presumably acquired the infection in the Valencia Region). We thus included patients admitted to Fontilles or notified to the Valencia Region registry from January 1940 to December 2015, who had clinical onset after 1940 and who were born in the Valencia Region. We excluded patients born abroad or outside the Valencia Region, or with a record of travel abroad to any leprosy endemic country at any time before clinical onset. Patients with no data on region of birth (nine patients) or date of clinical onset (two patients) were also excluded.

Incidence rates were expressed per 100,000 population per year, and were calculated as the number of patients having clinical onset during a given time period, divided by the population at the median point of the period and the number of years within each period. Age distributions of cases with onset in successive decades were analysed using beanplots, which show individual observations for each period along with their respective averages and density distributions.¹⁷

The sex ratio was calculated as the ratio of incidence in males to the incidence in females. The MB/PB classification was extracted from the clinical records according to the clinical description of the lesions, neurological damage, slit skin smears and biopsy, where available. For cases prior to 1988, the disability grade was determined on the basis of the recorded clinical description.

The 'municipality of origin' was defined as the municipality of birth when this information was available; in the cases for which no municipality of birth was registered, it was defined as the municipality of residence; in the cases for which no municipality of birth or residence was registered, it was defined as the municipality where the leprosy diagnosis was made.

All analyses were performed in Stata version 13.1 (StataCorp, College Station, TX, USA). Figure 3 was done with R version 3.2.5. Maps were produced with ARCGIS 10. The study was approved by the Ethics Committee of Hospital Universitario La Paz.

Results

A total of 442 patients (275 from Fontilles database and 151 additional patients from the Valencia Region registry) were born in the Valencia Region and had clinical onset after 1940. After excluding 16 patients who had travelled abroad before the date of clinical onset, 426 patients were included in the Valencia region with presumably autochthonous leprosy.

INCIDENCE RATES AND TRENDS

The numbers of cases and incidence rates by onset period are shown in Table 1, for the Valencia Region and each of its three provinces; 109 (25.6%) patients originated in Alicante, 89 (20.9%) patients in Castellón and 228 (53.5%) patients in Valencia.

The numbers of new patients declined steadily over the period from 1940 to 2006 (Figure 2). There were no new cases reported having clinical onset after 2006.

AGE DISTRIBUTION

The birth dates ranged from 1865 to 1973 (two patients had missing birth dates). The median age at onset was 33 years (range 3 to 81 years; IQR 23 to 50 years) and two patients had

Table 1. Number of leprosy cases and annual incidence rates per 100,000 population in the Valencia Region, by onset date. Results are shown for the three provinces and for the whole Valencia Region, divided by province (1940–2012) ($n = 426$)

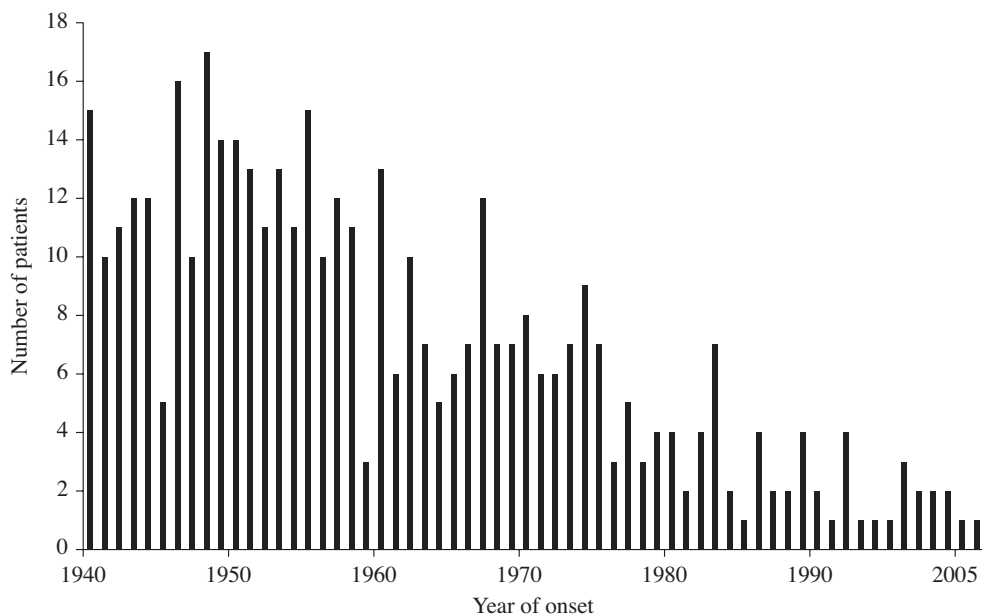
Year of onset	Alicante		Castellón		Valencia		Total Valencia Region	
	N	Incidence	N	Incidence	N	Incidence	N	Incidence
1940–49	42	0.677	18	0.565	62	0.476	122	0.544
1950–59	19	0.282	36	1.084	58	0.418	113	0.472
1960–69	20	0.245	13	0.359	47	0.294	80	0.288
1970–79	15	0.145	15	0.367	28	0.146	58	0.174
1980–89	9	0.072	5	0.114	18	0.086	32	0.085
1990–99	2	0.014	2	0.043	9	0.041	13	0.032
2000–15	2	0.009	0	0.000	6	0.019	8	0.013

missing age at onset. Mean age at onset gradually increased from 34.2 years during the period 1940–1949 to 59.5 years during the period 2000–2015. The age distributions by period of onset are shown in Figure 3.

SEX RATIO

Two hundred and forty-six patients (57.7%) were male, and 180 (42.3%) were female. The sex ratio according to year of onset is shown in Table 2.

There was a male predominance consistently across all periods of onset, with no clear trend with time, although it was highest in the last time period, but the number of cases was low in that period.

**Figure 2.** Number of patients by year of clinical onset ($N = 426$).

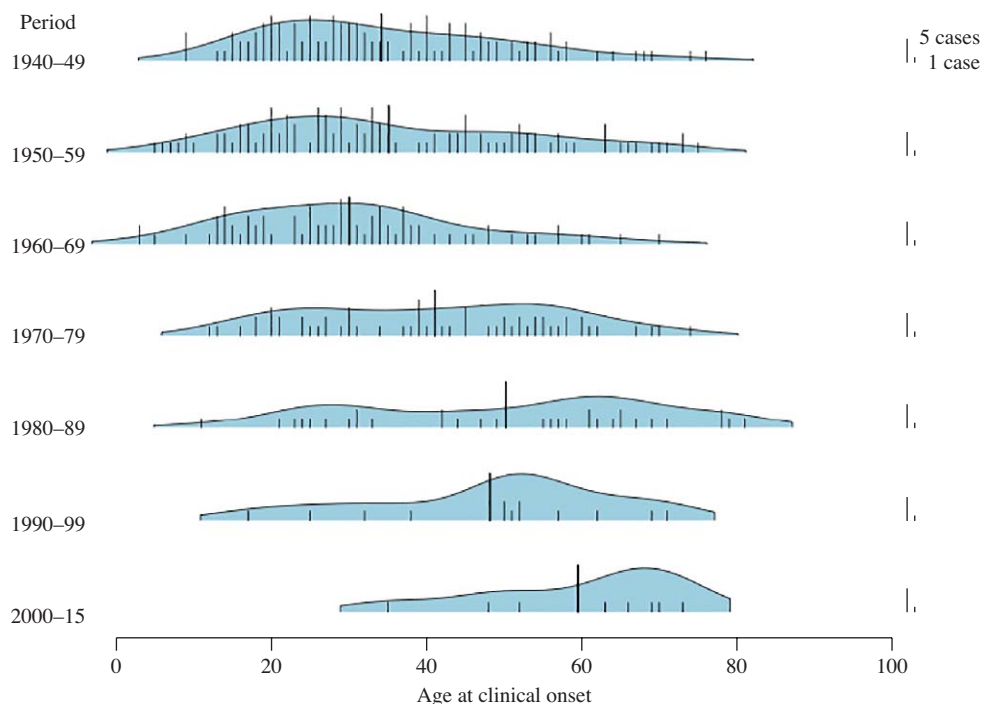


Figure 3. Age distributions at clinical onset of autochthonous leprosy cases in the Valencia Region by period of clinical onset, 1940–2015. Mean ages are shown as thick lines and relative frequency distributions (density estimation) as shaded areas.

CLASSIFICATION

Three hundred and sixty-three patients (85.4%) were MB and 62 (14.6%) were PB. In one patient the classification was unknown. The proportion of MB did not differ significantly between males and females: 86.9% of the males and 83.3% of the females were MB. The average age at diagnosis was 36.3 (SD 17.1) years for MB cases and 39.3 (SD 19.1) years for PB cases. Since the year 1970, the proportion of MB by year of onset gradually increased over time from 74.1% in 1970–79 to 87.5% in 2000–2015 (Figure 4).

Table 2. Number of leprosy cases and incidence rates (per 100,000 population) in the Valencia Region, by onset date, divided by sex (1940–2015) ($n = 426$)

Onset date	Male cases	Male incidence (per 100,000)	Female cases	Female incidence (per 100,000)	Sex ratio
1940–49	65	0.606	57	0.487	1.24
1950–59	69	0.600	44	0.354	1.69
1960–69	40	0.296	40	0.280	1.06
1970–79	36	0.219	22	0.128	1.71
1980–89	22	0.120	10	0.052	2.29
1990–99	8	0.041	5	0.024	1.66
2000–15	6	0.020	2	0.007	3.07

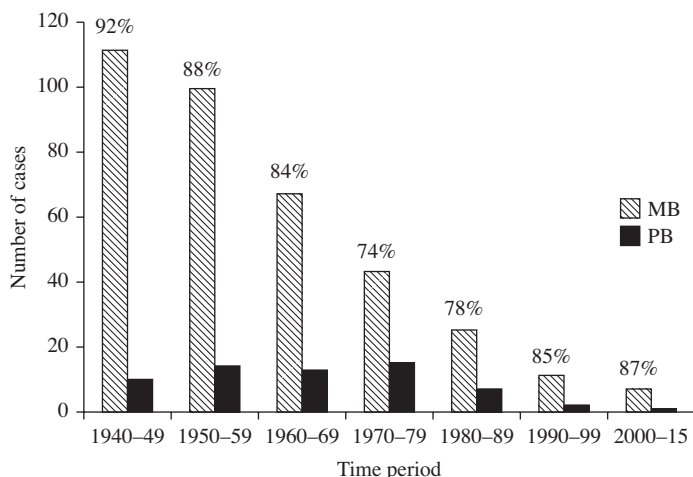


Figure 4. Number of cases by MB – PB classification, by year of onset ($n = 425$). The proportion of MB cases among all cases diagnosed in each time period is shown over each bar.

OCCUPATIONS

Information on occupation was available for 264 patients. The majority of male patients worked in agriculture, and the majority of female patients were housewives (Table 3).

DISABILITIES

Among the 231 (52.2%) patients with information on disability at diagnosis, 128 (55.4%) had no disability, 59 (25.5%) had Grade 1 disability and 44 (19.1%) had Grade 2 disability. There seemed to be a trend for males to have a higher proportion with disabilities than females, although this was not statistically significant. MB cases had significantly higher proportion of Grade 1 and 2 disabilities than PB cases (Table 4).

CONTACT HISTORY

Information on (putative source) contacts was only reliably recorded for the 275 patients in the Fontilles database: 186 (67.6%) patients had a known leprosy contact. Among the 275 patients with information on contacts, 139 (50.5%) had family contacts and 64 (23.3%) had

Table 3. Occupation of the patients, divided by sex

Occupation	Male: n (%)	Female: n (%)	Total
Housewife	0 (0)	91 (83.5)	91 (34.5)
Agriculture	99 (63.9)	8 (7.3)	107 (40.5)
Commercial	2 (1.3)	4 (3.7)	6 (2.3)
Student	4 (2.6)	2 (1.8)	6 (2.3)
Manual workers	40 (25.8)	4 (3.7)	44 (16.7)
Other	10 (6.4)	0 (0)	10 (3.8)
Total	155	109	264

Table 4. Proportion of patients with disabilities according to sex and MB/PB classification

Disability	Sex (n, %)			Classification (n, %)		
	Male	Female	p	MB	PB	p
Grade 0	74 (51.7)	54 (61.4)	0.297*	99 (51.6)	29 (76.3)	0.016*
Grade 1	38 (26.6)	21 (23.9)		54 (28.1)	4 (10.5)	
Grade 2	31 (27.7)	13 (14.8)		39 (20.3)	5 (13.2)	

* χ^2 test for heterogeneity (two-tailed).

non-family contacts. The proportions of patients who reported family and non-family known leprosy contacts is shown in Figure 5.

Though the proportion of patients reporting family or any (family and non-family) contact did not change consistently over time, we note that, among the 275 patients for which contact information was available, both cases with onset since 2000 had a history of family contact, as did obvious outliers in age in Figure 3 (all patients under 50 in the period 1980–1989 and the 17 year old with onset in 1990).

GEOGRAPHIC DISTRIBUTION

Information on municipality of birth was available for 275 patients. Among the remaining 151 patients, information on municipality of birth was not available so either the municipality of residence (in six patients) or the municipality of diagnosis (in 145 patients) was used as a proxy. In this manner, all 426 patients were assigned a municipality of origin.

Figure 6 shows the temporal trends of the annual incidence of autochthonous leprosy by municipality of origin in 20-year periods. Most of the cases, especially during the later periods, were concentrated in the coastal regions.

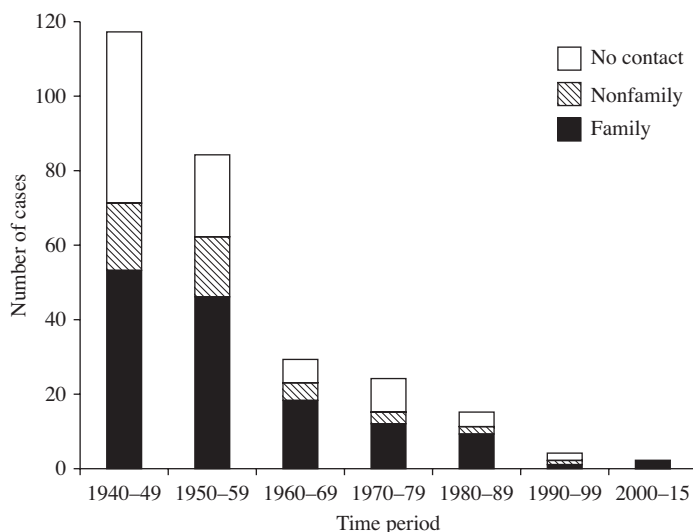


Figure 5. Number of patients with recorded family, non-family or no known leprosy contact by onset date from Fontilles database ($n = 275$).

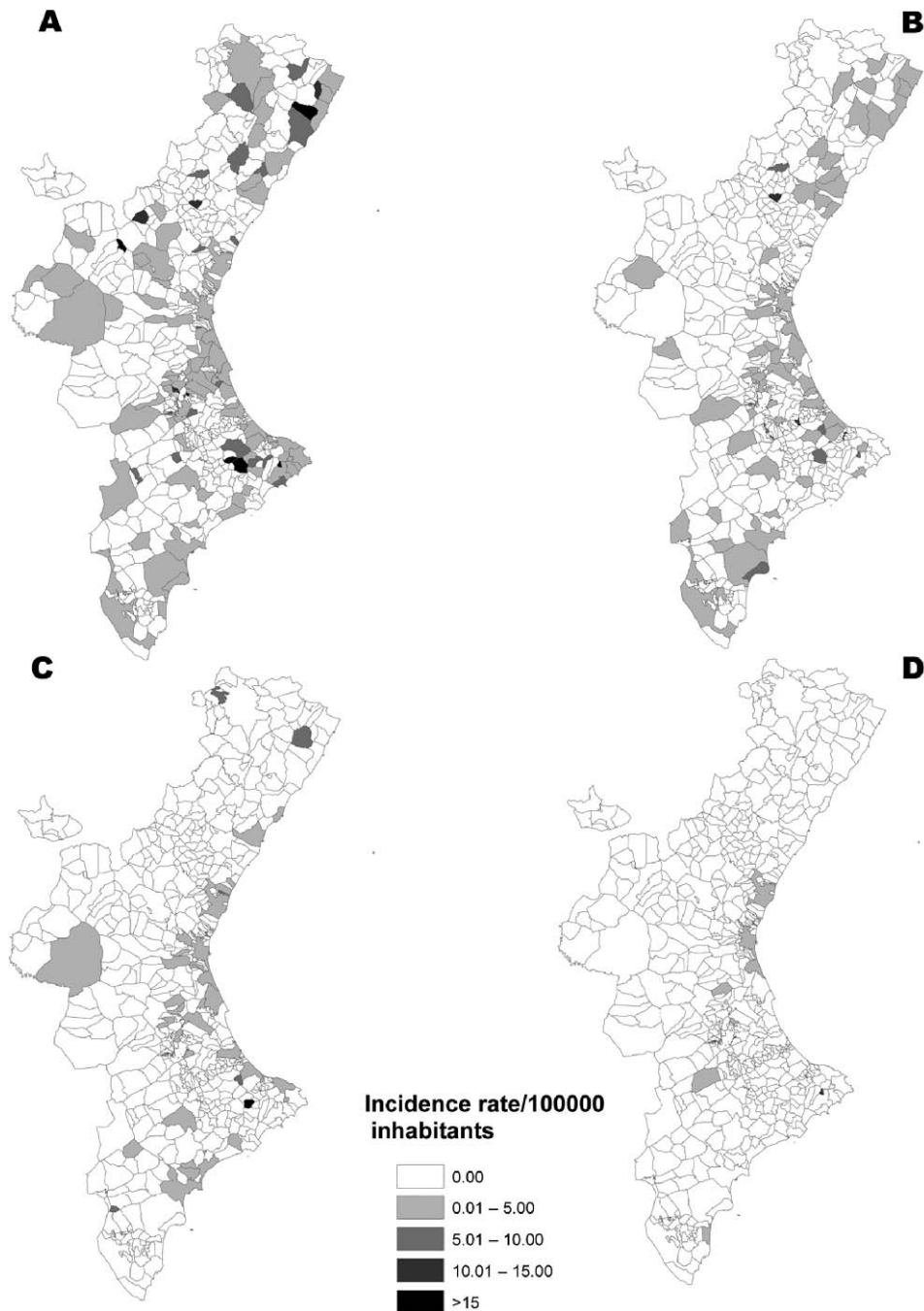


Figure 6. Annual incidence of autochthonous leprosy (per 100,000 population) by municipality of origin and time period: A) 1940–59, B) 1960–79, C) 1980–99 and D) 2000–15 (426 cases).

In order to explore whether different patterns became evident using municipality of diagnosis as a proxy for municipality of origin, municipality of birth and municipality of diagnosis were compared in 86 patients for which both variables were available. Forty-two out of 86 patients had identical municipality of birth and diagnosis; for the remaining 44 patients, the municipality of diagnosis was very close geographically in 23 of them. To further explore this, we repeated the maps for cumulative incidence and the temporal trends by 20-year periods only for 275 the patients for which the municipality of birth was available (data not shown): the geographic distribution was similar.

Discussion

This study has analysed the patterns and trends of autochthonous leprosy in the Spanish Valencia Region since 1940, during which period the incidence rates steadily declined. As found by other studies in regions with declining incidence rates, we have found that average age at onset increased with time. Autochthonous leprosy in this region has had a male predominance, a high proportion of multibacillary cases and, among males, has been diagnosed mainly in agricultural workers.

As in our study, previous research in countries with declining incidence rates has consistently found a shift toward older age groups with time.^{10–13,18} Although this could be explained in part by a later age at infection due to a lower risk of exposure as incidence declines, analyses of successive birth cohorts suggest that the main explanation for this trend is an increase over time in the proportion of cases with longer incubation periods.¹⁰ The changes in age distribution in the Valencia Region, along with the fact that there have been no cases with onset after 2006 and no cases among persons born after 1973 (assuming that our data are complete), are consistent with a dramatic decline in transmission of *M. leprae* and suggest that transmission has effectively stopped in this region.

The decline in incidence started at least by 1940–1950, well before multidrug therapy was available. As in other Spanish regions, several changes happened in the Valencia Region that might explain this decline, such as rapid urbanisation, a decline in agriculture, and socioeconomic improvement. Previous studies in Spain and elsewhere have linked a decrease in leprosy incidence to improvements in education, housing conditions and increase in gross domestic product (GDP).^{4,19–20} Other factors that could have influenced this decline include increases in numbers of health centres and in mobile teams (which performed active contact tracing), the institution of a universal healthcare system, and the Fontilles hospital which provided isolation and access to drug treatment for all leprosy patients.

Our study revealed an increase in the proportion of patients with MB leprosy since the year 1970, perhaps analogous to trends described in other studies;¹⁰ though this trend was not clear over the years before 1970. These trends should be interpreted with caution as there were changes in the classification system over this period. We did not find a convincing increase over time in the male-to-female ratio, which has been described in some populations with declining incidence rates, but this trend has not been found as consistently as increases in age at onset.¹⁸

One might expect that the proportion of cases with close family or household contact would increase as leprosy disappeared from a population, insofar as any risk factors for transmission or disease expression are likely to be shared with closest contacts. The quality of the data on this aspect was good, as information on contacts was systematically collected in

Fontilles, though we cannot exclude some degree of concealment of known contacts due to concerns about social stigma. The proportion of cases reporting known contacts was high in this series. Though we may not see a consistent trend over time (Figure 5), we do note that, for those patients with available contact information, both cases with onset since 2000 with information on possible contacts reported family contact, and the obvious young outliers in Figure 3 (the 17 year old with onset in 1990 as well as all patients under 50 years of age in the period 1980 – 89) had known family contact. Such observations are consistent with current understanding of leprosy epidemiology.

We found a very high proportion of male patients working in agriculture: 64% throughout the whole study period, which is much higher than the proportion of agricultural workers in the general population: among the male general population, the proportion of agricultural workers in the Valencia Region steeply decreased from 54% in 1940 to 34% in 1960, and since then gradually to 6% in 2010.¹⁶ This finding is consistent with previous evidence that leprosy may be more frequent in rural than urban areas,^{11,14,21–22} and suggests that environmental factors should be further investigated. A rural predominance might not be expected given that *M. leprae* transmission is thought to be largely by a close contact or respiratory route, which should be particularly associated with crowded urban environments. Possible explanations for a rural predilection could include an animal or some other environmental reservoir (the recent recognition of *M. leprae* in squirrels in the UK illustrates this possibility²³) or some factor associated with lifestyle in rural areas.^{14,24} The geographic distribution also seemed to have a predominance for coastal areas. An association of leprosy incidence with coastal regions has been reported previously in Norway²² and Portugal.¹¹

A potential limitation of our study is the possibility of underestimation of new cases due to underreporting (but this is unlikely as notification of new leprosy cases is compulsory in Spain), or underdiagnosis due to lack of awareness of health staff (which might be more likely in recent years as the disease has declined and health workers have become less familiar with it).

In conclusion, we have studied the patterns and trends of autochthonous leprosy during the last seven decades in an endemic region in eastern Spain with declining incidence. This is the first study that has analysed these trends in Spain, and its results are broadly concordant with findings from other regions with declining incidence rates. Our results suggest that the transmission of *M. leprae* infection in this area may well have now stopped. The geographic distribution and the high incidence in agricultural workers suggest that environmental factors should be further explored.

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Contributors

ISG designed the study, analysed the data, drafted the paper, and is the guarantor. JRGE and FMC collected the data. DGB performed the spatial analysis and produced the maps. PF asked the research question, suggested the study, advised on the protocol and analysis and assisted in drafting the paper. All authors were involved in interpretation of the data and commented on interim drafts. All authors have read and approved the final version of the article.

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