INTERNATIONAL JOURNAL OF LEPROSY

Volume 73, Number 4
Printed in the U.S.A.
(ISSN 0148-916X)

Factors Contributing to the Decline of Leprosy in Spain in the Second Half of the Twentieth Century

José L. Alfonso[1], Fernando A. Vich[2], Juan J. Vilata[3], J. Terencio de las Aguas[4]

ABSTRACT

Background: Leprosy is a chronic infectious disease that is considered to be declining, though it still remains prevalent in many parts of the world. A study was made to explore the health and socioeconomic factors that most influenced the trend of the disease in a typical Mediterranean country.

Materials and methods: An ecological study was conducted, investigating possible social, economic and health factors related to the evolution of leprosy incidence. The time period considered was 50 years—the second half of the twentieth century in Spain.

Results: The variables showing the strongest correlation to evolution of the incidence of the disease were employment, the number of physicians, and the gross domestic product (GDP), with negative coefficients—while tuberculosis showed a positive coefficient. However, the GDP showed the highest coefficient (0.5). The model that best explained the evolution of leprosy over the last 50 years comprised a 6-year lag period between the socioeconomic factors and the incidence of leprosy—explaining 57% of the data obtained. The annual decrease in leprosy incidence was 1.6%.

Conclusions: Socioeconomic development, assessed in terms of the GDP, was the most important factor in explaining the evolution of leprosy incidence.

RÉSUMÉ

Contexte: La lèpre est une maladie chronique considérée comme étant sur le déclin, bien qu'elle reste encore prévalente dans plusieurs régions du monde. Le but de cette étude fut d'explorer dans un pays méditerranéen typique, les facteurs sanitaires et socio-économiques qui ont eu le plus d'impact sur l'évolution épidémiologique de la maladie.

Matériel et méthode: Une étude écologique étudiant les facteurs sanitaires, économiques et sociaux en relation avec l'évolution de l'incidence de la lèpre fut menée en considérant un intervalle de temps de 50 années - la deuxième moitié du 20ème siècle - en Espagne.

Résultats: Les variables qui ont montré les corrélations les plus robustes avec l'évolution de l'incidence de la maladie furent l'activité, le nombre de médecins, et le Produit Intérieur Brut (PIB), avec des coefficients négatifs - tandis que la tuberculose montrait un coefficient positif. Cependant le PIB a montré le plus haut coefficient (0,5). Le modèle qui a le mieux prédit l'évolution de la lèpre au cours de ces 50 dernières années fut celui ayant un décalage de 6 années entre les facteurs socio-économiques et l'incidence de la lèpre - donnant une explication pour 57% des données acquises. Le taux de diminution annuel de l'incidence de la lèpre a été de 1,6%.

Conclusions: Le développement socio-économique, évalué à l'aide du PIB, était le facteur le plus important pour expliquer l'évolution de l'incidence de la lèpre.

RESUMEN

Background: Aunque la lepra es una enfermedad infecciosa crónica en decaimiento, aún permanece vigente en muchas partes del mundo. El presente, es un estudio realizado con el fin de explorar los factores de salud y sanitarios que tienen más influencia en la tendencia de la enfermedad en un típico país Mediterráneo.

[1] Servicio de Medicina Preventiva, Consorcio Hospital General Universitario de Valencia.
[2] Centro Salud Pública de Manises, Consellería de Sanidad de la Comunidad Valenciana.
[3] Servicio de Dermatología, Consorcio Hospital General Universitario de Valencia.
[4] Advisor to the International Leprosy Association (ILA).

Name and address to whom requests for reprints should be addressed: José L. Alfonso MD, Ph.D., Servicio de Medicina Preventiva, Consorcio Hospital General Universitario de Valencia, Departamento de Medicina Preventiva y Salud Pública, Universidad de Valencia, Blasco Ibáñez 15, 46010 - Valencia (Spain); e-mail: jose.l.alfonso@uv.es

Material y Métodos: Se realizó un estudio ecológico en el cual se investigaron los posibles factores sociales, económicos y sanitarios relacionados con la evolución de la incidencia de la lepra. El periodo de tiempo considerado fue de 50 años -la segunda mitad del siglo XX en España.

Resultados: Las variables que mostraron alta correlación con la evolución de la incidencia de la enfermedad fueron el desempleo, el número de médicos, y el producto doméstico bruto (PDB), con coeficientes negativos -la tuberculosis, en cambio, mostró un coeficiente positivo. El PDB mostró el coeficiente más alto (0.5). El modelo que mejor explicó la evolución de la lepra en el periodo de 50 años analizado comprendió un periodo lag de 6 años entre los factores socioeconómicos y la incidencia de lepra - explicando el 57% de los datos obtenidos. La disminución anual en la incidencia de lepra fue del 1.6%.

Conclusiones: El desarrollo Socioeconómico, medido en términos del PDB, fue el factor más importante para explicar la evolución de la incidencia de lepra.

Leprosy is a chronic infectious disease produced by *Mycobacterium leprae* that results from an imbalance between the bacterium and the host immune response. With a history that goes back three thousand years, leprosy is one of the oldest diseases known.

For centuries, the care of leprosy patients lacked a scientific basis. Affected individuals were isolated from society and from their couples, and diseased children were separated from their families. Later, scientific evidence came to show that in some cases isolation is not particularly effective, and that no more than 5% of exposed individuals actually develop the disease.

In its third regional conference of leprosy, the World Health Organization (WHO) proposed elimination of the disease as a health problem in all countries by the year 2005. However, the number of new cases documented by the WHO in 2003 totaled 513,798, while the prevalence of the disease that same year was 457,792 cases. In other words, leprosy is still far from being controlled, and work remains to be done before the disease can be relegated to the history books. The majority of cases of leprosy are found in Southeast Asia. The present annual incidence of the disease worldwide is almost one new patient per minute, and is fundamentally attributable to developing countries like India—with 70% of all such cases. Some studies have even reported the incidence of the disease to be increasing in these parts of the world ([25]).

One of the principal factors relating to control of the disease, and which was already suspected many years ago, is the social and economical development of society. In this context, it has been shown that economical development is accompanied by important improvements in patient quality of life (QoL), and a decrease in mortality ([3]).

Although the incidence of leprosy in Spain has decreased greatly, thanks to factors such as economical development, and the prevalence of the disease has also decreased in recent years, a minimum number of fundamentally imported cases remain ([7, 21]), as a result of which it is difficult to speak of actual eradication of the disease.

The present study explores the influence of socioeconomic factors in the evolution of leprosy in Spain—a country illustrative of the Mediterranean setting of the disease in the last 50 years.

MATERIALS AND METHODS

Two leprosy information sources have been used: the Spanish State Leprosy Registry (*Registro Estatal de Lepra*), a database of the National Epidemiology Center (*Centro Nacional de Epidemiología*) ([6]), located in the *Instituto de Salud Carlos III* in Madrid, and which came into operation in 1991; and the Annual Statistical Bulletin (*Anuario Estadístico*) of the National Institute of Statistics (I*nstituto Nacional de Estadística, INE*) ([11]) for prior data up until the year 1950.

Economic (national income) data and their provincial distribution were in turn obtained from the publications of the Service of Studies of the *Banco de Bilbao Vizcaya* ([1]) (presently *BBVA*). Demographic information was collected from the Natural Variations of the Spanish Population (*Movimiento Natural de la Población Española*) ([12]), and from the Spanish population census ([13]), both being publications of the *INE*. The latter document reflects the data corresponding to the population censuses conducted every decade.

The variables derived from these information sources were classified into four groups. Variables to be included were required to remain stable in terms of both the information sources and the way in which they were obtained during the 50-year period covered by the study.

The data were obtained at the provincial level, followed by grouping according to the different Spanish Autonomous Communities. The selected socio-demographic variables were: the proportion of rural population (i.e., the percentage of the population not living in the capital versus the total population), the employment rate with respect to the total population (per thousand), the emigration rate, the schooling rate (defined as the proportion of the population in the 6–14 years age range in school versus the total population), and the unemployment rate.

As economical variables, the gross domestic product (GDP) per inhabitant was recorded, along with the product per educational and health sectors. The magnitudes of the economical variables were determined for each year at constant price, using the GDP deflactor, and employing the 1986 prices as reference (expressed in euros). The variable corresponding to health care resources was the proportion of physicians per 1000 inhabitants, and the health variables were the infant mortality rate, the incidence of leprosy per 100,000 inhabitants, and the incidence of respiratory tuberculosis (TBC) per 1000. Base 100 index numbers were used for both the GDP and the incidence of leprosy and TBC. Retrospectively, the 5-year elasticity was calculated based on the ratio between the 5-year incidence variations and the economical variations corresponding to the same period.

The statistical analyses included, a complete study of the type of distribution, followed by simple and multiple regression, residues analysis with the Kolmogorov-Smirnov test for one sample, and correlation between typified residues. Likewise, the co-linearity between variables was studied based on eigenvalues, the condition index and proportions of variance. Finally, fitting was carried out based on logarithmic transformation of the data and co-linearity study via the tolerance, variance inflation factor (VIF), and also the study of residues—including histograms of typified residues and dispersion plots.

In practice, exact co-linearity is rarely observed in studies of this kind, though so-called "near co-linearity" is seen with some frequency (i.e., some variable is found to be "nearly" a linear combination of another variable/s). We have jointly applied the method proposed by Kleimbaum ([18]) and the criteria of Belsley ([2]). The latter author proposes utilization of the condition indices and proportion of variance decomposition to conduct the analysis of co-linearity—establishing a value of 0.5 as the upper proportion threshold, as a result of which the conclusions are finally reached as follows: high condition indices (over 30) indicate the number of co-linearities, and their magnitude reflects their relative importance. If a given component possesses a condition index of over 30, and two or more variables present a high proportion of variance in the latter, then these variables are considered to be co-linear. Taking into account the long incubation period of leprosy (generally between 2–10 years) ([26]), the incidence rates were studied with the socioeconomic status of the population 1–10 years previously, i.e., at the time of contagion.

RESULTS

Regarding the mean annual incidence rates for leprosy, established for 5-year periods and 100,000 inhabitants during the period 1950–2000 (Fig. 1), and the interannual variations (Table 1), important differences are seen among the different regions. In effect, while most regions show reductions at a rate of 1% annually, some actually end up showing increases—such as the Balearic Islands, Navarra, and the Basque Country. Andalucía, in the south of the country, for many years exhibited the highest leprosy incidence for that period, though it is also the Spanish Autonomous Community with the greatest interannual reductions (almost 4.5%), followed by Galicia—with reductions of 3%—and the Canary Islands and Valencia (2%). Overall, Spain showed a decrease of 1.6% annually over this period of 50 years.

In Table 2 the longitudinal study by regions presents the mean values from 1950 to 2000 for the variables considered in the study. Differences between regions are clearly seen, with important variability in

TABLE 1. *Mean annual incidence (per 100,000) and inter-annual variation of leprosy in Spain by communities and nationwide, 1950–2000.*

	51–55	56–60	61–65	66–70	71–75	76–80	81–85	86–90	91–95	96–2000	%Variation*
ANDALUCÍA	2.41	1.79	1.24	1.03	0.23	0.79	1.38	0.89	0.38	0.2	–4.42
ARAGÓN	0.18	0.36	0.18	0.18	0.09	0	0	0.08	0	0.17	–0.02
ASTURIAS	0	0.21	0.2	0.1	0.1	0	0	0	0	0	0
BALEARIC ISLANDS	0	0	0	1.2	0	0.16	0.15	0	0	0.67	1.34
CANARY ISLANDS	1.26	1.61	0.42	0.66	0.09	0.38	2.08	1.3	0.31	0.31	–1.9
CANTABRIA	0.25	0	0	0	0	0	0	0	0	0	–0.5
CASTILLA LEON	0.1	0.21	0.25	0.33	0.04	0.08	0.12	0	0	0	–0.2
CASTILLA LA MANCHA	0.54	0.4	0.46	0.54	0.12	0.18	0	0.12	0.18	0.18	–0.72
CATALONIA	0.83	0.73	0.13	1.26	1.09	0.76	0.62	0.03	0.02	0.26	–1.14
VALENCIAN COMMUNITY	1.04	0.63	0.24	0.72	0.33	0.33	0.99	0.42	0.23	0.08	–1.92
EXTREMADURA	0.66	1.53	0.94	0.48	0.35	0.73	0.48	0.28	0	0	–1.32
GALICIA	1.23	0.38	0.19	0	0.08	0.11	0.15	0.15	0.11	0.26	–1.94
MADRID	0.21	0.04	0.04	0.09	0.11	0.23	0.02	0.06	0.04	0.1	–0.22
MURCIA	1.59	0.77	0.5	0	0.12	0.89	0.52	0.2	0	0.09	–3
NAVARRA	0	0.25	0	0	0.22	0.41	0	0	0	0.19	0.38
BASQUE COUNTRY	0.09	0.33	0.36	0.31	0.11	0.05	0.14	0	0	0.1	0.02
RIOJA	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0.38	n.a.
CEUTA/MELILLA	0	0	0	0	0	0	0	2.25	0.73	0	0
SPAIN	0.96	0.75	0.44	0.58	0.29	0.4	0.57	0.3	0.13	0.16	–1.6

Note: * = % inter-annual variation; n.a. = not available.

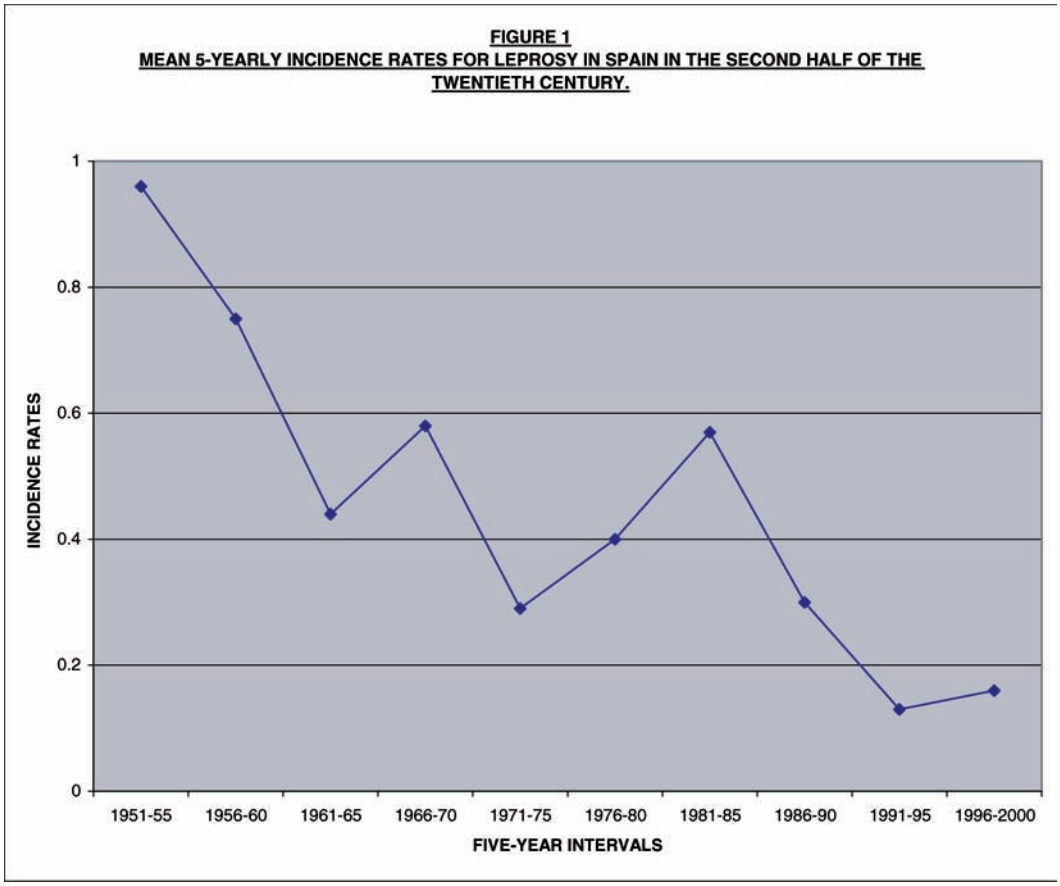

FIG. 1. Mean 5-yearly incidence rates for leprosy in Spain in the second half of the Twentieth Century. *Note:* Incidence rate = cases per 100,000.

both the economical values (with a nearly three-fold difference between minimum and maximum), and particularly the incidence of tuberculosis (with an up to 5.5-fold difference) and leprosy—the latter being the parameter showing the largest differences (up to 25-fold). In relation to this latter variable, the regions with the highest figures were Andalucía and Extremadura, along with Catalonia and the Canary Islands.

On the other hand, in relation to the 5-year means of the variables considered in the study by regions (Table 3), all Autonomous Communities were seen to exhibit a relatively regular evolution with gradual decreases or increases—the sole exception being emigration, which proved to be somewhat irregular.

In reference to 100 base index numbers of the Gross Domestic Product (GDP) and incidences for leprosy and tuberculosis in Spain (Table 4), a 7.23-fold economical increase was observed since the year 1950—this figure being similar to the reduction in the incidence of leprosy in the same period of time (7.4-fold). In turn, tuberculosis was seen to have decreased in incidence 3.7-fold in the course of the period 1950–2000. On the other hand, the mean annual variation in GDP was seen to be 14%, while the mean variations for leprosy and tuberculosis were quite similar (–1.66 and –1.57, respectively). The proportional variations taking economical growth as reference base revealed that leprosy varied –0.06 units for each proportional unit economical increment. The situation was similar in the case of tuberculosis (–0.07).

Considering that economical status exerts an influence at the time of actual contagion, even though clinically manifest leprosy only appears some years later, we evaluated

TABLE 2. *Annual rate per 100,000 inhabitants for all Spanish regions, 1950–2000.*

	Emigration	Employ-ment	Schooling	Physicians	Infant mortality	Unem-ployment	GDP	Rural population	Health product	TBC	Incidence of leprosy
ANDALUCÍA	4.84	30.78	12.59	2.02	0.49	40.01	3174	70	87	0.39	1
ARAGÓN	4.76	38.8	10.69	2.87	0.35	19.47	4503	54	124	0.24	0.12
ASTURIAS	2.94	38.61	10.82	2.21	0.34	28.63	4281	85	98	0.6	0.06
BALEARIC ISLANDS	2.4	44.54	12.14	2.19	0.25	31.31	6217	60	190	0.18	0.22
CANARY ISLANDS	4.77	34	12.68	1.79	0.45	37.97	4360	64	125	0.12	0.82
CANTABRIA	3.65	39.1	12.07	2.34	0.4	25.75	4442	68	109	0.48	0.02
CASTILLA LEÓN	5.59	37.41	12.84	2.29	0.64	21.28	3512	69	103	0.35	0.12
CASTILLA LA MANCHA	4.97	34.33	11.99	1.59	0.62	22.39	3037	85	67	0.23	0.29
CATALONIA	5.46	40.38	10.72	2.57	0.21	27.8	5986	63	193	0.21	0.54
VALENCIAN COMMUNITY	4.08	38.58	11.65	2.15	0.28	34.23	4738	70	123	0.18	0.47
EXTREMADURA	6.61	32.42	11.7	1.56	0.69	32.86	2472	86	69	0.34	0.58
GALICIA	7.61	41.7	11.69	1.72	0.43	24.52	3382	85	89	0.36	0.26
MADRID	3.63	37.76	10.84	3.45	0.31	29.17	6601	28	246	0.11	0.09
MURCIA	3.29	33.68	12.86	1.89	0.45	24.22	3682	70	87	0.25	0.43
NAVARRA	5.04	40.04	11.78	2.7	0.41	24.15	5208	69	179	0.35	0.11
BASQUE COUNTRY	5.58	37.92	11.38	2.48	0.27	32.31	5719	63	168	0.25	0.13
RIOJA	4.82	41.65	11.86	2.25	0.44	16.99	4799	63	125	0.26	0.04
CEUTA/MELILLA	7.78	22.03	10.86	1.63	0.47	27.33	2952	0	99	0.41	0.29

TABLE 3. *Corresponding annual rates for each of the factors analyzed in Spain, 1950–2000.*

Year	Emigration	Employment	Schooling	Physicians	Infant mortality	Unemployment	GDP(€)	%Rural population	Health product(€)	TBC	Incidence of leprosy
1950	1.97	41.09	7.38	1.04	1.28	6.25	1583	72.14	62.78	0.89	0.27
1955	1.51	40.43	9.92	1.1	1.01	5.22	1946	70.43	72.29	0.59	0.14
1960	1.09	39.83	12.27	1.15	0.76	4.26	2279	68.86	81.03	0.31	0.15
1965	8.17	39.04	11.68	1.25	0.56	4.59	2984	66.31	107.17	0.21	0.094
1970	14.55	38.33	11.16	1.34	0.37	4.88	3619	64	130.71	0.12	0.117
1975	9.52	35.73	13.1	1.98	0.22	26.63	4142	63.37	150.68	0.13	0.05
1980	5	33.4	14.85	2.56	0.09	46.2	4613	62.8	168.63	0.15	0.039
1985	2.57	33.69	13.59	3.24	0.08	54.51	5426	63.09	166.45	0.16	0.127
1990	0.23	33.97	12.38	3.89	0.08	59.59	6203	63.36	164.36	0.18	0.032
1995	4.65	35.82	9.51	4.12	0.06	62.16	9746	64.29	184.92	0.2	0.009
2000	4.27	37.79	6.32	4.42	0.04	38.45	13027	66.01	215.7	0.194	0.032

Notes: Units as for Table 2.
(€) = Euros. GDP and Health Product in constant prices based on 1986 and GDP deflator.

TABLE 4. *Index numbers corresponding to the evolution of leprosy and tuberculosis in relation to gross domestic product (GDP) in Spain, 1950–2000.*

Year	TBC	GDP Index number	Annual GDP variation	Incidence of leprosy	Leprosy Index number	Annual variation leprosy	Leprosy variation/economic variation	TBC	TBC Index number	Annual TBC variation	Economic variation/ TBC variation
1950	1583	100		0.27	100		–	0.89	100		–
1955	1946	122.88	22.88	0.14	51.85	–48.15	–2.10	0.59	66.29	–33.71	–1.47
1960	2279	143.91	21.03	0.15	55.56	3.71	0.18	0.31	34.83	–31.46	–1.50
1965	2984	188.43	44.52	0.094	34.81	–20.75	–0.47	0.21	23.60	–11.24	–0.25
1970	3619	228.53	40.1	0.117	43.33	8.52	0.21	0.12	13.48	–10.11	–0.25
1975	4142	261.58	33.05	0.05	18.52	–24.81	–0.75	0.13	14.61	1.12	0.03
1980	4613	291.32	29.73	0.039	14.44	–4.08	–0.14	0.15	16.85	2.25	0.08
1985	5426	342.62	51.3	0.127	47.04	32.6	0.64	0.16	17.98	1.12	0.02
1990	6203	391.73	49.11	0.032	11.85	–35.19	–0.72	0.18	20.22	2.25	0.05
1995	9746	615.39	223.67	0.009	3.33	–8.52	–0.04	0.2	22.47	2.25	0.01
2000	13027	822.93	207.54	0.032	11.85	8.52	0.04	0.19	21.35	–1.12	–0.01
Mean	5556		14.46	0.11		–1.66	–0.06	0.31		–1.57	–0.07

TABLE 5. *Logistic regression model for different forecast terms of leprosy in Spain, 1950–2000.*

	B Coefficient	R^2	Sig.
Lag 0	0.309	0.145	0.001
Lag 1	–0.005	0.284	0.000
Lag 2	–0.006	0.286	0.000
Lag 3	–0.012	0.291	0.000
Lag 4	–0.041	0.303	0.000
Lag 5	–0.096	0.312	0.000
Lag 6	–0.484	0.568	0.000
Lag 7	–0.201	0.282	0.000
Lag 8	0.001	0.166	0.000
Lag 9	0.108	0.192	0.012
Lag 10	0.102	0.157	0.130

the data on economic growth corresponding to the preceding years (1, 2, 3, etc.) in relation to the incidence of Hansen's Disease. To this effect we developed both simple and multiple regression models, using the annual information from all Spanish provinces. In this respect, Table 5 shows the results of multiple regression, fitted by Naperian logarithmic transformation. The explanatory contribution, measured in terms of R^2, is seen to increase until a 6-year lag was reached; at this point 57% of the incidence of leprosy was explained. Later, with increasing delays, the values began to decrease—though in an irregular manner.

In the multiple regression analysis, based on the model involving a 6-year lag and using the annual and provincial data, we in turn developed a complete model (Table 6). The results revealed that the factors seen to influence the incidence of leprosy were: employment, the number of physicians, and economic growth, all with negative coefficients, while tuberculosis was associated with a positive coefficient. Nevertheless, the GDP was found to yield the most important coefficient, with a value of 0.5, followed by infant mortality and the physician rate.

In view of the similar behavior of tuberculosis as regards economic growth, a study was made of the interactions and resulting co-linearity. In this context, tolerance and the variance inflation factor showed medium tolerance for the variables GDP, infant mortality and health education sector product, unemployment, and the number of physicians—while high tolerance was recorded for the rest.

DISCUSSION

The main problem posed by studies of this kind is that the data corresponding to the factors analyzed must offer continuity and reliability. This prevented us from examining a large number of variables which logically should have been included in the study.

The regions with the highest rate and most total cases of leprosy were Andalucía and Extremadura (both of which showed the lowest economic levels), followed by Catalonia and the Canary Islands—possibly due to the important number of immigrants found in these autonomous communities. Within Andalucía, the province of Córdoba clearly stands out—with a mean rate for the global study period of 0.6 new cases per 100,000 inhabitants per year—together with the province of Jaén ([7]) . In sum, a preferentially though somewhat irregular Mediterranean distribution is observed, in coincidence with the findings of other authors, in relation to the cases of leprosy ([26]).

On the other hand, although the study has been carried out with delimitations in the form of provinces and/or regions, the distribution of Hansen's disease is known to be extremely irregular—with marked intra-regional variations in Spain and also elsewhere in the world ([35]).

Since 1981, the World Health Organization (WHO) has recommended multi-drug therapy for the management of leprosy, and has considered it possible to eliminate the disease as a public health problem worldwide. The leprosy-eliminating strategy proposed by the WHO has been based on the hypothesis that a reduction in the prevalence of the disease based on the administration of multi-drug regimens (dapsone, clofazimine and rifampicin) entails a low reservoir of cases in the community (fewer than 1/10,000 inhabitants)—as a result of which the transmission cycle of the disease cannot be perpetuated ([25, 32]). The concept underlying this strategy is the so-called "basic reproduction rate, R_0" (the mean number of individuals directly infected by an infectious case). If R_0 is >1, an epidemic may result, while if R_0 is <1, the disease may disappear. In the case of leprosy, it has been estimated that R_0 is <1 when the prevalence rate is less than 1/10,000—a situation that has been applicable in Spain for many years. In our study the observed

TABLE 6. *Conditioned factors analysis of the trend of leprosy in Spain, 1950–2000 (logarithmic regression).*

	B COEFFICIENT	*t*	Sig.	ULCI	LLCI	TOLERANCE	VIF
Emigrant	0.241	1.52	0.129	–0.04	0.27	0.35	2.88
Employment	–0.174	–3.05	0.002	–3.59	–0.78	0.56	1.78
Schooling	0.024	0.48	0.631	–0.82	1.36	0.73	1.37
Physician	–0.202	–3.47	0.001	–0.34	–0.09	0.80	1.25
Infant mortality	0.238	1.82	0.068	–0.01	0.04	0.99	1.01
GDP	–0.484	–4.67	0.000	–2.45	–1.01	0.17	5.91
Rural population	0.018	0.31	0.754	–0.69	0.96	0.53	1.87
Health product	0.015	0.14	0.886	–0.82	0.95	0.16	6.25
Tuberculosis	0.150	6.04	0.000	0.26	0.51	0.23	4.40

Note: B = beta, t = t Student, Sig. = significance, ULCI = upper limit confidence interval, LLCI = lower limit confidence interval,
VIF = variance inflation factor

annual reduction rate was 1.6%, while some sources in the literature conclude that countries with endemic disease have annual reduction rates of 4% ([23]).

However, certain data and contradictions speak against the optimism of the WHO and raise doubts as to the evolution of the disease—questioning the central argument of the elimination strategy whereby the only effective contagion source is the lepromatous patient, and a reduction in prevalence therefore necessarily implies a reduction in incidence. The principal unsettled questions refer to the evidence suggesting a slightly decreasing general incidence (though not in all countries); uncertainty over the true number of individuals with occult infection; a lack of knowledge of the magnitude of the problem posed by subclinical carriers of the disease ([20]); and the possible existence of animal reservoirs ([5, 36]). Many authors consider that the disease found in armadillos and monkeys is different from that seen in humans ([27]). Another important consideration is the present lack of an effective vaccine ([10]).

In this context, and in an attempt to account for the evolution of leprosy, sociosanitary and economic considerations have been postulated to be of greater relevance than multitherapy. In favor of this hypothesis would be the declining trend of the disease in China and Spain starting before implementation of the WHO multi-drug strategy, and the spontaneous disappearance of the disease in Norway ([24]), Japan ([15]) and Hawaii ([37]), as well as its continued persistence in India, Brazil ([17]) and Cuba despite application of the WHO program. In the case of Norway, the gradual decrease in leprosy incidence was accompanied by an increase in mean patient age at appearance of the disease, and a gradual prolongation of the incubation period ([24]).

Leprosy prevalence data were not used in this study, because they posed concordance problems with the incidence data. Such discordance was mainly due to the repetition of individuals included in the prevalence lists. Moreover, while the incidence rate was not affected as a result, the prevalence rates were falsely elevated due to persistence in the prevalence lists of cases that had likely died or healed.

Although the regression analysis cannot consider only the sum of the effects of variables, since the interference factors absorb part of the explanation or prediction of changes in the incidence of leprosy, the interactions among variables do not seem to be sufficiently intense to compromise interpretation of the results. The same applies to the co-linearity among variables assessed by variance inflation factors and tolerance. The confounding variables and resulting attributable bias always pose a considerable risk and are a source of imprecision in ecological studies, due to the scant control afforded by the use of population instead of individual measures ([29]).

Although some authors have reported tuberculosis to be antagonistic to leprosy, attributing the almost total disappearance of the latter to the appearance of tuberculosis, it must be considered that this is an infectious disorder, and that the environmental

conditions and factors of hygiene are therefore the bases for transmission. In this sense, socioeconomic status could be essential for creating a setting unfavorable for the transmission of both diseases, as observed in our study.

Previous authors have addressed the possible relationship between socioeconomic development and concrete health aspects, e.g., mortality in the classical study of Krishnan ([19]) in India, or Mckeown ([22]) in England; or neonatal mortality in the study of Shah and Abbey ([33]) in Baltimore (United States), among many others. However, a review of the literature has yielded almost no studies relating socioeconomic development to the evolution of leprosy incidence. In contrast, analyses have been made of the social and economic variations observed in leprosy patients, and the need to restore such parameters to their previous levels in order to help heal the patients, as in a published Indian study ([29]). Other parameters investigated include crowding, domestic conditions, family size ([31]), and even the inverse relation between years of schooling and the incidence of leprosy in a study from Malawi ([28]).

The present study made use of the gross domestic product (GDP), as recommended by some authors for conducting medium- and long-term studies ([9]). In this context, GDP was seen to be the factor exerting the greatest influence upon leprosy evolution, according to the multiple regression analysis with a 6-year lag period. It should be taken into account that economic development is the fundamental factor influencing family crowding conditions, schooling, and other factors such as nutritional status ([33]), likewise related to the incidence of leprosy. The family grouping of leprosy observed in some studies may also be a consequence of shared socioeconomic status (and therefore hygiene conditions) ([16]). Therefore some authors recommend considering this as a factor in chronic diseases ([35]).

The other two factors with negative and statistically significant coefficients were employment and the number of physicians, and the sum of their beta-coefficients was lower than that of GDP—i.e., they were seen to jointly exert much less influence upon leprosy incidence trends. The fourth significant factor was tuberculosis; in effect, since the latter is also a transmissible disease, it is also affected by social and economic development. Moreover, it should be taken into account that the results of the present study showed a similar interannual change for both transmissible diseases, and that Bacillus Calmette Guérin (BCG) vaccination produces a certain degree of immunity against leprosy as well ([8, 38]).

In relation to the lag period used to explain the incubation period of leprosy, the estimated period is 2.9 to 5.3 years in the case of tuberculoid leprosy, and 9.3 to 11.6 years in the case of the lepromatous form of the disease—though in our study a period of 6 years was seen to afford the best explanation for the observed statistical relationship. Other authors have reported periods of up to 30 years in veterans—a situation not examined in the present study.

It may have been advisable to separate the cases according to the type of leprosy, to establish the possible differences in the influence of socioeconomic factors according to the type of disease involved. However, the incidence rates would have been zero or very close to zero in the last years of the study period.

The declining tendency of leprosy in Spain was seen to be gradual since the 1950s, i.e., it started before the introduction of multi-drug therapy, and was more closely associated with the socioeconomic development of the country. Similar observations also apply to a number of other European countries ([14]), in addition to Norway as noted above ([24]). Our study illustrates the multicausal model of effects, whereby socioeconomic considerations can prove more important than the actual transmissibility conditions of leprosy.

REFERENCES

1. Banco Bilbao Vizcaya. Renta Nacional de España y su Distribución Provincial. Años 1950 a 1995. Servicio de publicaciones.
2. Belsley, D. Detecting and assessing the problems caused by multi-collinearity: A use of the singular-value decomposition. No. 66 in NBER Working Papers, National Bureau of Economic Research, Inc., 1974.
3. Bhattacharya, S. N., and Sehgal, V. N. Leprosy elimination campaign and its impending fallout. Int. J. Dermatol. **39**(9) (2000) 667–669.
4. Bjarnason, O. The last lepra patient in Iceland. Nord. Medicinhist. Arsb. (1989) 197–203.
5. Bruce, S., Schroeder, T. L., Ellner, K., Rubin, H., Williams, T., and Wolf, J. Armadillo exposure and Hansen's disease: an epidemiologic sur-

vey in southern Texas. J. Am. Acad. Dermatol. **43**(2 Pt. 1) (2000) 223–228.
6. Centro Nacional de Epidemiología. Manual del registro estatal de lepra. Madrid. Instituto de Salud Carlos III. 1991.
7. Delgado-Rodriguez, M., Rodriguez-Contreras Pelayo, R., Extremera-Castillo, F., Serrano-Ortega, S., and Galvez-Vargas, R. Epidemiologic aspects of leprosy in the province of Jaen. Rev. Clin. Esp. **185**(2) (1989) 99–103.
8. Fine, P. E. M. Variation in protection by BCG: implications of and for heterologous immunity. Lancet **346** (1995) 1339–1345.
9. Getzen, T. E. Forecasting health expenditures: short, medium, and long term. J. Health Care Finance **26**(3) (2000 Spring) 56–72.
10. Gupte, M. D., Vallishayee, R. S., Anantharaman, D. S., Nagaraju, B., Sreevatsa, Balasubramanyam S., de Britto, R. L., Elango, N., Uthayakumaran, N., Mahalingam, V. N., Lourdusamy, G., Ramalingam, A., Kannan, S., and Arokiasamy, J. Comparative leprosy vaccine trial in south India. Indian J. Lepr. **70** (1998) 369–388.
11. Instituto Nacional de Estadística. Anuario estadístico Ministerio de Economía. Madrid. Años 1950 hasta 2001.
12. Instituto Nacional de Estadística. Censo de la población española. Ministerio de Economía. Madrid. Años 1950 hasta 2000.
13. Instituto Nacional de Estadística. Movimiento natural de la población española Ministerio de Economía. Madrid. Años 1950 hasta 2001.
14. Irgens, L. M., Melo-Caeiro, F., and Lechat, M. F. Leprosy in Portugal 1946–80: epidemiologic patterns observed during declining incidence rates. Lepr. Rev. **61**(1) (1990) 32–49.
15. Ito, I. The epidemiological situation in south east Asia. Lepr. Rev. **52** (1981) 43–51.
16. Jain, S., Reddy, R. G., Osmani, S. N., Lockwood, D. N., and Suneetha, S. Childhood leprosy in an urban clinic, Hyderabad, India: clinical presentation and the role of household contacts. Lepr. Rev. **73** (2002) 248–253.
17. Kleinbaum, D. G., Kupper, Ll., and Morgenstern, H. Epidemiologic research: Principles and quantitative methods. New York: Van Nostrand Reinhold. 1982.
18. Krishnan, P. Mortality decline in India. 1951–1961: developmental versus public health program hypothesis. Soc. Sc. Med. **9** (1975) 475–479.
19. Lechat, M. F. The source of infection: an unsolved issue. Indian J. Lepr. **72** (2000) 169–173.
20. Lockwood, D. N., and Suneetha, S. Leprosy: too complex a disease for a simple elimination paradigm. Bull. World Health Organ. **83** (2005) 230–235.
21. Lopez-Velez, R., Saez-Vaquero, T., Blanco-Arevalo, J. L., and Gomez-Mampaso, E. Leprosy simulating other diseases. Rev. Clin. Esp. **199** (1999) 369–372.
22. McKeown, T., and Brown, R. G. Medical evidence related to English populations change in the eighteenth century. Pop. Stud. **9** (1965) 119–123.
23. Meima, A., Gupte, M. D., van Oortmarssen, G. J., and Habbema, J. D. F. Trends in leprosy case detection rates. Int. J. Lepr. Other Mycobact. Dis. **65** (1997) 305–319.
24. Meima, A., Irgens, L. M., Van Oortmarssen, G. J., Richardus, J. H., and Habbema, J. D. Disappearance of leprosy from Norway: an exploration of critical factors using an epidemiological modelling approach. International Journal of Epidemiology **31** (2002) 991–1000.
25. Meima, A., Richardus, J. H., and Habbema, J. D. Trends in leprosy case detection worldwide since 1985. Lepr. Rev. **75** (2004) 19–33.
26. Noordeen, S. K. Descriptive epidemiology of leprosy. In: *Leprosy*. Hasting eds. Edimburgh. Churchill Livingstone Publications, 1985.
27. Noordeen, S. K. Toward the elimination of leprosy, the challenges and opportunities. Int. J. Lepr. Other Mycobact. Dis. **66** (1998) 218–221.
28. Ponnighaus, J. M., Fine, P. E., Sterne, J. A., Malema, S. S., Bliss, L., and Wilson, R. J. Extended schooling and good housing conditions are associated with reduced risk of leprosy in rural Malawi. Int. J. Lepr. Other Mycobact. Dis. **62** (1994 Sep) 345–352.
29. Rao, V. P., Rao, I. R., and Palande, D. D. Socio-economic rehabilitation programmes of LEPRA India—methodology, results and application of needs-based socio-economic evaluation. Lepr, Rev. **71** (2000) 466–471.
30. Rothman, K. J., and Greenland, S. *Modern Epidemiology*. Philadelphia. 2nd ed. Lippincott Williams & Wilkins, 1998.
31. Saikawa, K. The effect of rapid socio-economic development on the frequency of leprosy in a population. Lepr. Rev. **52** (1981) 167–175.
32. Sansarricq, H. Epidémiologie de la lèpre. In: *La lèpre*. Chapitre 5. Paris. Edit Ellipses Universités francophones, 1995, pp. 54–72.
33. Shah, F., and Abbey, H. Effects of some factors on neonatal and postneonatal mortality. Milbank Mem. Fund Q **49** (1971) 33–57.
34. Skinsnes, O. K. Effect of malnutrition on leprosy. Int. J. Lepr. Other Mycobact. Dis. **44** (1976) 374–375.
35. Terencio de las Aguas, J. La lepra, pasado, presente y futuro. Valencia. Ed Generalitat Valenciana, 1999, pp. 57–75.
36. Valverde, C. R., Canfield, D., Tarara, R., Esteves, M. I., and Gormus, B. J. Spontaneous leprosy in a wild-caught cynomolgus macaque. Int. J. Lepr. Other Mycobact. Dis. **66** (1998) 140–148.
37. Worth, R. M. The disappearance of leprosy in a semi-isolated population (Nihau Island, Hawai). Int. J. Lepr. Other Mycobact. Dis. **31** (1963) 34–35.
38. Zodpey, S. P., Bansod, B. S., Shrikhande, S. N., Maldhure, B. R., and Kulkarni, S. W. Protective effect of Bacillus Calmette Guérin (BCG) against leprosy: a population-based case-control study in Nagpur, India. Lepr. Rev. **70** (1999) 287–294.