INTERNATIONAL JOURNAL OF LEPROSY
and Other Mycobacterial Diseases

OFFICIAL ORGAN OF THE INTERNATIONAL LEPROSY ASSOCIATION

EDITORIAL OFFICE
National Hansen's Disease Center
Carville, Louisiana 70721, USA

VOLUME 53, NUMBER 4 DECEMBER 1985

EDITORIALS

Editorial opinions expressed are those of the writers.

Secular Trends in Leprosy: Increase in Age at Onset Associated with Declining Rates and Long Incubation Periods

For several reasons, a decline of incidence rates in many leprosy-endemic areas may be in the offing. The 1970s and 1980s have seen an upsurge in leprosy research concomitant with the inclusion of leprosy among the six diseases selected by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. At the same time, considerable efforts are being made to increase the effectiveness of the health services in many of the countries involved, both in general and in the field of leprosy. Also, general living conditions have improved in many areas. Of most significance, irrespective of the causes, is the continuous decline of leprosy rates already being observed in a number of affected countries, a trend which hopefully will continue into the future and also spread to other countries. The scope of the present article is not to enlarge on the causes of a possible decline but, rather, to focus on epidemiologic patterns to be observed during declining incidence rates.

In leprosy, the establishment and operation of patient registers with a high case ascertainment have involved considerable problems: in part, the necessary infrastructure in many areas has been lacking; in part, leprosy is a disease involving negative social stigma leading to avoidance of registration. Thus, the evaluation of secular trends or, in other words, the assessment of whether or not an observed decline in rates represents a true secular trend, constitutes a difficult task. Accordingly, as recommended by a WHO study group,[1] all information available should be utilized in attempting to establish robust epidemiological indicators useful in the evaluation of secular trends. This information has to be searched for in areas in which a considerable decline has already been observed and documented.

During the last few centuries, Norway is the only country in which leprosy has been completely eradicated. From 1856, the epidemiological situation has been documented by the National Leprosy Registry of Norway,[2, 3] the first register ever to have

[1] World Health Organization. Epidemiology of leprosy in relation to control. Tech. Rpt. Ser. 716. Geneva: WHO, 1985.

[2] Irgens, L. M. and Bjerkedal, T. Epidemiology of leprosy in Norway: the history of the National Leprosy Registry of Norway from 1856 until today. Int. J. Epidemiol. **2** (1973) 81–89.

[3] Irgens, L. M. Leprosy in Norway. An epidemiological study based on a national patient registry. Lepr. Rev. **51** Suppl. (1980) 1–130.

been established for any disease. This collection of data, pertaining to 8231 patients, provides unique possibilities to enlighten situations encountered during declining incidence rates. Later, a considerable decline also registered in other countries,[4–10] and a basis evolved for the assessment of general patterns.

Since World War II, in developed countries tuberculosis has been a disease of the higher ages. The well-established negative association between age at onset and risk has even led to the inclusion of age as a variable in the system of selection used by the national register of selective chest x-ray examinations in Norway, covering all inhabitants older than 15 years. Toward the end of the endemic in Norway, leprosy was also a disease particularly attacking old people. Furthermore, a shift in age at onset was observed concomitant with the declining incidence rates (Fig. 1).[3]

From a theoretical point of view, two mechanisms may be responsible for this negative association between mean age at onset and incidence rate observed in both tuberculosis and leprosy. On the one hand, it is evident that the risk of being taken ill by a disease caused by environmental factors is dependent upon the level of environmental factors as well as the duration of the exposure to the environment. Thus, when the level of the factors is high, e.g., when the prevalence of infectious cases is high, a person has to live a shorter life to reach the exposure necessary to initiate the pathogenesis. In such a situation, age at infection and thus also age at onset will inevitably be lower compared with a situation in which a person has to live a longer life to reach the same amount of exposure. This mechanism may be involved during stable conditions without fluctuations in incidence rates and may explain the observations in India suggesting that mean age at onset is low when incidence rates of leprosy are high and vice versa[11]; and the mechanism may just as well explain the shift toward higher age groups observed when incidence rates are declining.

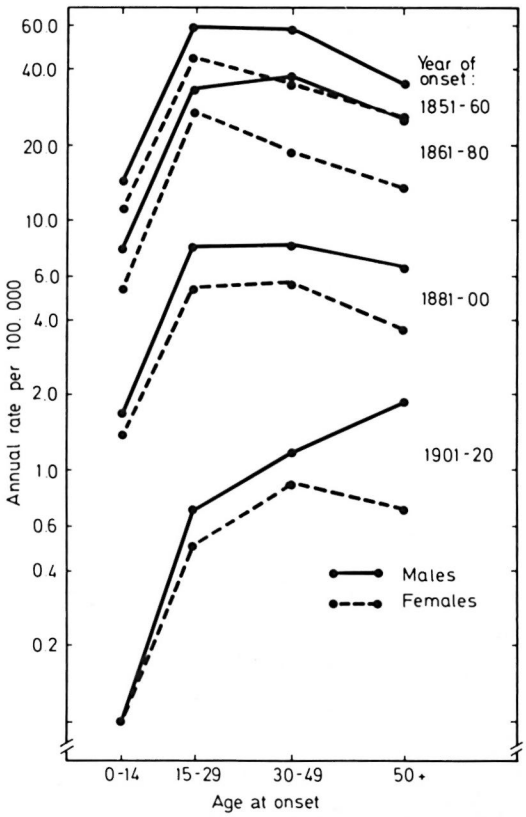

FIG. 1. Incidence rates of leprosy in Norway, 1851–1920. Age- and sex-specific rates by year of onset.[3]

On the other hand, however, a different mechanism related to the long and varying incubation period in leprosy may cause the same effect without implying a shift in age

[4] Davey, T. Decline of leprosy in a group of Nigerian villages between 1941 and 1956. Int. J. Lepr. **25** (1957) 329–344.

[5] Feldman, R. and Sturdivant, M. Leprosy in Louisiana, 1855–1970. An epidemiologic study of long-term trends. Am. J. Epidemiol. **102** (1975) 303–310.

[6] Ito, T. The epidemiological situation in South East Asia. Lepr. Rev. **52** Suppl. (1981) 43–51.

[7] Li, H. Y., Pan, Y. L. and Wang, Y. Leprosy control in Shandong Province, China, 1955–1983; some epidemiological features. Int. J. Lepr. **53** (1985) 79–85.

[8] Saikawa, K. The epidemiological phenomenon on decreasing tendency of leprosy disease. Jpn. J. Lepr. **50** (1981) 99–104.

[9] Vanderverken, M., Lechat, M. F., Misson, C. B., Vellut, C. and Antony, V. V. Age-, sex-, type-specific incidence rates in leprosy. Observation on 45,000 leprosy patients detected in Polambakam, South India, over a 27-year period. Abstract in Int. J. Lepr. **53** (1985) 740.

[10] Zuniga, M. and Castellazzi, Z. 30 años de evolución de la endemia de la lepra en Venezuela (1949–1979). Caracas: Cepialet, 1982.

[11] Christian, M. The epidemiological situation of leprosy in India. Lepr. Rev. **52** Suppl. (1981) 35–42.

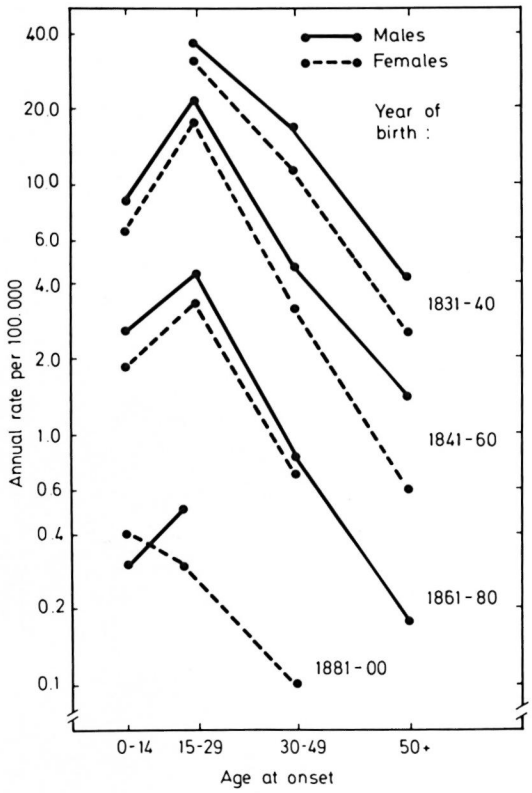

FIG. 2. Incidence rates of leprosy in Norway, 1851–1920. Age- and sex-specific rates by year of birth.[3]

at infection to older age groups.[12] During declining incidence rates, patients with long incubation periods, who were infected when the level of exposure was higher, will be relatively more numerous than patients with shorter incubation periods, who were infected during lower levels of exposure. Thus the patients with long incubation periods will inevitably be older.

Thus, two mechanisms may be responsible for the increasing age at onset observed when incidence rates are declining. To the extent the first mechanism is involved, age at infection would increase and thus age at onset in consecutive birth cohorts would necessarily increase. The second mechanism, however, is not based on a change in age at infection and would not imply changes in age at onset in consecutive birth cohorts. This mechanism might even mask a decrease in age at onset in consecutive birth cohorts.

Cohort analyses based on data from Norway have contributed to the clarification of the issue. No increase in age at onset was observed in consecutive birth cohorts (Fig. 2).[3] The trend, if anything, seemed to follow the opposite direction: in consecutive birth cohorts a decrease in age at onset was observed. This is consistent with the fact that when incidence rates are declining, the only risk of getting infected and developing disease in a late birth cohort would exist early in life. Later the risk is much lower or even nonexistent, as in Norway today.

The question then arises: to what extent do these findings correspond with observations in other countries? Areas under epidemiological surveillance for long periods reporting age at onset or age at registration, and where a considerable decline in the occurrence of leprosy has taken place, are found in Japan,[6,8] United States/Louisiana,[5] Nigeria/Ndi Oji Abam,[4] Venezuela,[10] India/Polambakam,[9] and China/Shandong.[7] To compare patterns observed in a situation of decline and under stable conditions, great interest would attach also to a temporal series of age-specific rates registered in countries without a decline in incidence rates. Unfortunately, it seems that no such series have yet been published.

The question of the extent to which the observations in Norway correspond to those in other countries has been addressed in a recent publication.[12] Admittedly, the data reported and analyzed are based on different systems of surveillance (Table 1). Some schemes report case detection rates or even incidence rates by year of onset, and the data are acquired through national or provincial registries, implying a well-organized local system of registration, treatment, and follow-up. In other areas, the information provided concentrates on the number of new cases per year in addition to data on the total population. The schemes also differ as to the numbers of patients forming the bases of the rates reported, ranging from a few hundred to almost 50,000. Thus, great differences in the accuracy of the rates are involved.

Nevertheless, the data are considered suf-

[12] Irgens, L. M. and Skjaerven, R. Secular trends in age at onset, sex ratio and type index in leprosy observed during declining incidence rates. Am. J. Epidemiol. **121** (1985) 695–705.

TABLE 1. *Administrative and epidemiological data from schemes for surveillance of leprosy in eight areas, covering a substantial decline in rates.*[12]

Country	Area under surveillance	Authors	Period of surveillance	Period of decline		No. new patients from t_0 until t_n	Rate (per 10,000)		Relative decline i_0/i_n	Annual relative decline $\sqrt[y]{i_0/i_n}$
				t_0	t_n		i_0	i_n		
China	Shandong Province	Li, Pan and Wang[7]	1955–	1958	1979	20,368	0.50[a]	0.02[a]	25.2	1.17
India	Polambakam	Vanderverken and Lechat[8]	1955–	1955	1981	45,000	134.0[b]	9.9[b]	13.5	1.11
							MB[c] 30.8	0.3	102.7	1.20
							PB[d] 97.1	8.1	12.0	1.10
Japan	Mainland	Ito[6]	1907–	1950	1980	5,553	0.092[e]	0.0016[e]	57.5	1.15
Japan	Okinawa	Saikawa[8]	1907–	1967	1980	1,014	1.81[b]	0.17[b]	10.7	1.20
Nigeria	Ndi Oji Abam	Davey[4]	1941–1956	1941–1945	1952–1956	303	132.0	20.0	6.6	1.19
Norway	West and North Norway	Irgens[2]	1851–	1851–1860	1911–1920	6,509	3.34[a]	0.03[a]	111.3	1.08
U.S.A.	"French Louisiana"	Feldman and Sturdivant[5]	1855–	1905–1914	1955–1964	684[f]	0.120	0.007	17.1	1.07
Venezuela	Entire country	Zuniga and Castellazzi[10]	1951–	1951	1980	17,365	1.596[b]	0.238[b]	6.7	1.07

[a] Incidence rates (by year of onset).
[b] Case detection rates (by year of registration).
[c] MB = multibacillary.
[d] PB = paucibacillary.
[e] Rates calculated on the basis of number of new cases reported.
[f] All patients in the study.

TABLE 2. *Data on age at onset in leprosy from eight areas in which a substantial decline in rates has been recorded.*[12]

Area	Measure	Subgroup	Observation periods	
			1955–1959	1975–1979
China	RR[a] age $\frac{60+}{0-14}$	Males	1.8	17.0
		Females	1.3	10.3
			1962–1966	1977–1981
India	RR age $\frac{40-69}{5-14}$	Multibacillary	4.4	17.3
		Paucibacillary	0.5	0.6
			1956–1962	1975–1980
Japan, Mainland	Percentage, age groups	70+	4.4%	26.0%
		0–29	23.9%	10.0%
			1966–1970	1976–1980
Japan, Okinawa	Percentage, age groups	65+	8.0%	21.1%
		0–14	22.6%	8.8%
			1941–1943	1953–1955
Nigeria	Percentage, age groups	50+	5.9%	15.0%
		0–14	33.3%	15.0%
			1851–1960	1911–1920
Norway	RR age $\frac{50+}{0-14}$	Males	2.4	21.9
		Females	2.3	9.6
		Multibacillary	2.0	17.8
		Paucibacillary	2.9	14.3
			1900–1909	1960–1969
U.S.A.	Age group with peak incidence		50–59	80–89
			1951	1981
Venezuela	RR age $\frac{65+}{0-14}$		4.0	17.6

[a] Relative risk.

ficient to the purpose, i.e., to measure the decline in incidence in each area and to assess gross trends in the distribution of new cases by age. In particular, the remarkable continuity of leprosy control work in all the areas under surveillance secures uniformity in registration which is very important in studies of temporal trends.

In this analysis,[12] period of decline, n, was defined as the interval between the observation of the highest rate, i_0 at t_0, and the last observation, i_n at t_n. In all series, a continuous fall was observed throughout the period of decline which, however, covered a wide range. Thus, the relative decline i_0/i_n, was not fit for comparisons between countries, and the annual relative decline

$$\bar{r} = \sqrt[n]{i_0/i_n}$$

was used instead as a comparable measure. The annual relative decline ranged between 1.20 and 1.07. Most of the countries involved had a more rapid decline than that observed in Norway, which may be considered encouraging.

In Norway, the ratio old (50+)/young (0–14) increased by a factor of 9.1 (21.9/2.4) in males and 4.2 (9.6/2.3) in females (Table 2). In all of the other areas, a shift toward older age groups was observed as well (Table 2). In China, where a relatively high annual decline was observed, the shift toward older age groups was most pronounced; the ratio old (60+)/young (0–14) increased by a factor of 9.4 in males and 7.9 in females. After only a ten-year decline, this shift was already evident, e.g., in Nigeria[4] and Japan.[8]

Certainly it may be argued that a biased

TABLE 3. *Data on type index in leprosy from eight areas in which a substantial decline in rates has been recorded.*[12]

Area	Measure	Subgroup	Observation periods	
			1955–1959	1975–1979
China	Multibacillary	Males	35.5%	46.9%
	Total	Females	39.5%	47.1%
India	Lepromatous		1955	1980–1981
	Lepromatous + tuberculoid		24.1%	3.6%
Japan, Mainland	Lepromatous + borderline		1964–1968	1974–1980
	Total		62.7%	73.3%
Japan, Okinawa	Lepromatous		1966–1970	1976–1980
	Total		41.9%	60.8%
Nigeria	Lepromatous		1941–1943	1953–1955
	Total		3.9%	—
			1851–1960	1901–1920
Norway	Lepromatous	Males	63.4%	72.2%
	Lepromatous + tuberculoid	Females	63.9%	51.6%
U.S.A.	Not specified			
Venezuela	Lepromatous + borderline		1951	1981
	Total		36.3%	75.0%

case detection may effect a similar shift in age at onset. Thus, an improving effectiveness in case finding would perhaps give the result that more old patients, usually retired from the community at large, were detected. On the other hand, reduced efforts in case finding would effect a longer period of delay between onset and registration, which also would give a shift toward older age groups. However, many of the results reported are based on year of onset rather than year of registration, and thus this problem is to some extent circumvented.

On this basis, the conclusion seems pertinent that a shift toward older age groups during declining incidence rates is a general pattern in leprosy. Thus, age at onset is an important measure useful in the evaluation of secular trends. The measure is applicable also in areas with low case ascertainment and even in a clinical setting. Furthermore, a shift toward older age groups may be expected after a decline of only one decade and, on the other hand, if a shift is observed then the decline may be considered a reliable trend. Finally, the importance of noting age at onset is evident. The argument that age at onset is, in many cases, unknown is frequently encountered. However, the alternative, to use age at registration, will always give misleading results.

The epidemiological background or cause of this shift in age at onset has been further clarified by various studies. In the United Staes of America,[5] no shift toward older age groups was observed in consecutive birth cohorts; rather, the opposite seemed to occur. In a recent study from China,[7] this pattern is confirmed. Thus, it seems evident that changes in age at onset are not caused by a postponement of the infection to an older age. The old patients, taken ill after a considerable decline in incidence rates, represent cases with long incubation periods and are getting more and more frequent compared to patients with shorter incubation periods taken ill at the same time.

In general, lepromatous cases have a longer incubation period than the rest of the leprosy cases.[13] When the fraction of new cases with long incubation periods increases, the type index (the fraction of the new cases with lepromatous leprosy) will increase. Thus, an increase in type index concomitant with decreasing incidence rates

[13] Fine, P. E. M. Leprosy: The epidemiology of a slow bacterium. Epidemiol. Rev. **4** (1982) 161–188.

TABLE 4. *Simple and multiple regression of difference between leprosy incidence rates in two subsequent periods (secular trend) on mean age at onset, sex ratio, and type index in seven Norwegian counties.*[3]

Independent variables	Regression line	Level of significance	Correlation coefficient
X_1 (mean age at onset)	$\bar{Y} = 3.84 - 0.09X_1$	$p < 0.01$	−0.68
X_2 (sex ratio)		$p > 0.05$	−0.24
X_3 (type index)		$p > 0.05$	0.01
X_1X_3	$\bar{Y} = 3.07 - 0.09X_1 + 1.4X_3$	$p < 0.01$	0.70
$X_1X_2X_3$	$\bar{Y} = 3.33 - 0.10X_1 + 0.01X_2 + 0.01X_3$	$p < 0.01$	0.70

most likely represents another general principle in leprosy. This trend was observed in China,[7] Japan,[6,8] Venezuela,[10] and in Norwegian males[3] (Table 3).

In the interpretation of these observations, possibilities of biased case findings should also be taken into account. Toward the end of an endemic, efforts in case finding may be reduced and the less malignant cases may be overlooked, also causing a high type index. On the other hand, toward the end of an endemic an increasing resistance to leprosy in the population may be expected, causing the decline of incidence rates. If this resistance also is decisive as to the differentiation into clinical forms, lepromatous cases may become more and more rare. These two conflicting mechanisms may be related to the ambiguous observation in Norway, and to the inverse trend observed in India. Accordingly, type index may prove more controversial as an index for the evaluation of secular trends which, to a major extent, should be based on age at onset.

Thus, in multivariable regression analyses based on data from Norway, and with the decline in incidence rates defined as the dependent variable, the association with mean age at onset was far stronger than that with type index or with sex ratio, which was used as the third independent variable (Table 4).[3] Furthermore, the step-wise inclusion in the analysis of the latter variables did not significantly improve the goodness of fit, implying that from a statistical point of view the assessment of secular trends should be based on age at onset alone. Finally, it appeared that the index constructed on the basis of these analyses proved of great help in the assessment of secular trends; 76.6% of the situations were correctly classified as to decline or not, which was significantly different from a random classification ($p < 0.005$).[3] Certainly such an index should be evaluated on the basis of data from other countries. Also, the construction of an index for general use should preferably include data from more than one country. However, the schemes of control and follow-up now run in many countries, and particularly the OMSLEP recording and reporting system for leprosy patients recommended by WHO,[14] no doubt will produce data of great value for the establishment and evaluation of such an index, which should be pursued in the future.

On the other hand, the rationale behind the use of age at onset as a basis for an index to evaluate secular trends is essentially applicable to all infectious diseases with long and varying incubation periods. Tuberculosis, as the disease of the old, has already been mentioned. Also for this disease, there are no indications that infection is postponed to older ages as incidence rates are declining. As early as 1930, Andvord[15] arrived at that conclusion aided by cohort analysis of data from Norway, apparently one of the first cohort analyses undertaken in the history of epidemiology. Similar results were obtained in the U.S.A. by Frost in 1939.[16] In 1961, when tuberculosis no longer represented a major health problem in Norway, the secular trends, based on

[14] Lechat, M. F., Misson, C. B. and Walter, J. *OMSLEP Recording and Reporting System for Leprosy Patients.* 2nd ed. Brussels: Epidemiology Unit, Catholic University of Louvain, 1983.

[15] Andvord, K. F. Hvad kan vi lære ved å følge tuberkulosens gang fra generasjon til generasjon? Norsk Magasin for Lægevidenskab **91** (1930) 642–660.

[16] Frost, W. H. Age selection of mortality from tuberculosis in successive decades. Am. J. Hyg. **30** (1939) 91–96.

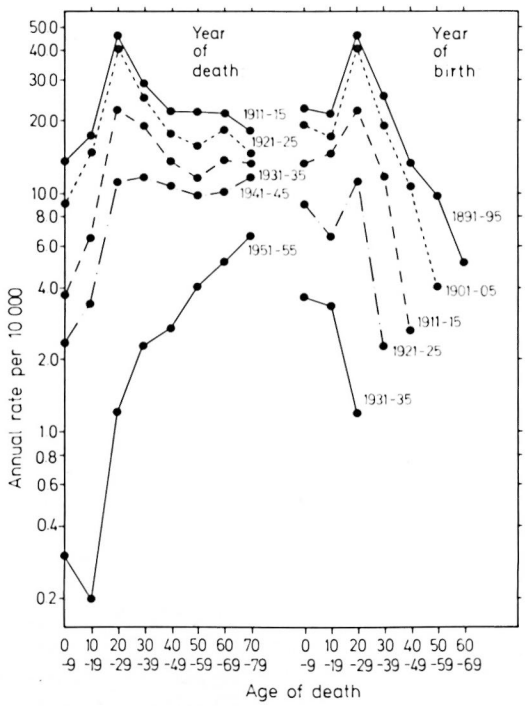

FIG. 3. Mortality rates of tuberculosis in Norway, 1891–1955. Age-specific rates by year of death and by year of birth.[17]

mortality rates in age at death by year of death and by year of birth, were analyzed by Backer (Fig. 3).[17] The findings of Andvord and Frost were confirmed, and the trends were even similar to those obtained for leprosy in Norway as well as in China.

There is reason to believe that this mechanism, relevant in leprosy and tuberculosis, plays a part in the epidemiology of any disease with a long and varying incubation period and caused by environmental factors. Certainly, in the surveillance and control of many of these diseases, e.g., the neoplastic diseases, there is no urgent need for special indices in the assessment of secular trends; in developed countries, at least, reported incidence rates are considered fairly reliable. On the other hand, the length of the incubation period in such diseases is often unknown. Thus, if a decrease is observed in the incidence of one of these diseases, e.g., like that occurring in carcinoma of the stomach,[18] a basis for mathematical simulations is established, taking possible changes in age at onset into account and aiming at the assessment of the length of the incubation period.

—Lorentz M. Irgens, M.D.

Institute of Hygiene
and Social Medicine
University of Bergen
5016 Haukland Sykehus
Bergen, Norway

[17] Backer, J. Trend of mortality and causes of death in Norway 1856–1955. Central Bureau of Statistics of Norway, 1961.

[18] Bjelke, E. The recession of stomach cancer: selected aspects. In: *Trends in Cancer Incidence.* Magnus, K., ed. Washington, D.C.: Hemisphere Publishing Company, 1982, pp. 165–181.