The impact of multidrug therapy on the epidemiological pattern of leprosy in Juiz de Fora, Brazil

O impacto da poliquimioterapia no perfil epidemiológico da hanseníase em Juiz de Fora, Brasil

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Abstract *We investigated the impact of multidrug therapy (MDT) on the epidemiological pattern of leprosy in Juiz de Fora, Brazil, from 1978 to 1995. Evaluation of 1,283 medical charts was performed according to the treatment regimen used in two different periods. Following the introduction of MDT in 1987, prevalence of leprosy decreased from 22 patients/10,000 inhabitants to 5.2 patients/10,000 inhabitants in 1995. Incidence rate of leprosy was lower in period II (1987-1995) than in period I (1978-1986). Decreasing prevalence and incidence appear to be related to drug efficacy rather than decreased case identification, since both self-referred and professionally referred treatment increased markedly from period I to period II. For both periods, multibacillary leprosy was the most frequent clinical form of the disease (±68%), and the main infection risk factor identified was household contact. Leprosy is predominantly manifested in adults, but an increase in the number of very old and very young patients was observed in period II. The MDT program has been effective both in combating leprosy and in promoting awareness of the disease.*

Key words *Leprosy; Combination Drug Therapy; Prevalence; Epidemiology*

Resumo *Investigamos o impacto da poliquimioterapia (PQT) no perfil epidemiológico da hanseníase em Juiz de Fora, Brasil, de 1978 a 1995. Fizemos uma avaliação de 1.283 prontuários, de acordo com o esquema terapêutico adotado em dois diferentes períodos. Desde a introdução da PQT, em 1987, a prevalência da hanseníase caiu de 22 pacientes/dez mil habitantes para 5,2 pacientes/dez mil habitantes em 1995. A incidência da doença foi menor no período II (1987-1995) em comparação ao período I (1978-1986). A diminuição da prevalência e da incidência está mais relacionada à eficácia das drogas que a uma queda na identificação da infecção, já que tanto a procura espontânea quanto os encaminhamentos aumentaram significativamente do período I para o período II. Em ambos os períodos, a forma clínica mais freqüente foi a multibacilar (±68%), e o contato intradomicilicar foi o maior fator de risco conhecido associado à infecção. Um aumento de pacientes muito velhos ou muito novos foi observado no período II. Os resultados indicam que o esquema PQT tem sido eficaz no combate à hanseníase e tem aumentado a conscientização e o conhecimento da doença.*

Palavras-chave *Hanseníase; Quimioterapia Combinada; Prevalência; Epidemiologia*

Introduction

Leprosy is a chronic infectious disease that represents a major public health problem, affecting some 1.8 million people worldwide (WHO, 1994). An estimated 2 to 3 million individuals suffer from physical disabilities as a result of having contracted leprosy (Van Beers et al., 1994). Although it is one of the oldest diseases afflicting humans, the possibility of treatment and cure did not come until the advent of sulfones in the 1940s. However, the results of sulfone use proved unsatisfactory. Dapsone failed to prevent the growth of resistant bacillus (Dharmendra, 1986), and new potent drugs like clofazimine (Browne & Hogerzeil, 1962) and rifampicin (Opromolla et al. 1965; Levy et al., 1976) were unable to prevent spread of the disease when used as monotherapeutic agents. In 1981, the World Health Organization (WHO) began to recommend a multidrug therapy (MDT) of dapsone, clofazimine, and rifampicin. MDT was an effective strategy and allowed for reduced treatment times compared to monotherapy: from five to two years for the lepromatous (L) or dimorphous (D) multibacillary forms (MB) and from 2 years to 6 months for the tuberculoid (T) or indeterminate (I) paucibacillary forms (PB). MDT was introduced into Brazil in 1986 and was authorized for leprosy treatment in 1992.

Based on the efficacy of MDT for leprosy, WHO has targeted elimination of the disease as a worldwide public health problem by the year 2000. To do so, it has enrolled authorities from countries with high rates of the disease. Brazil currently has the second highest prevalence and incidence of leprosy in the world. The Brazilian government, through its State Health Departments, has been working to reduce prevalence of the disease to less than 1 case per 10,000 inhabitants, considered a low rate by WHO.

Juiz de Fora, a city with 414,520 inhabitants (population estimate for 1995), has many leprosy patients, but the disease's epidemiological pattern here has not been described to date. This article analyzes the main characteristics of leprosy in Juiz de Fora and investigates the impact of MDT on the disease's epidemiological pattern.

Patients and methods

Juiz de Fora is the home of a regional health office for the State of Minas Gerais and serves a large number of nearby cities by providing drugs and human resources for leprosy treatment and control. The city has two health centers providing care for people with leprosy: the "Dr. Antônio Carlos Pereira Filho" Dermatology Sector and the University Hospital. We studied the epidemiological patterns of leprosy patients over two defined periods, differing in their use of MDT and in some characteristics of the control program, as described in Table 1.

In the first phase of the study, the medical charts of 1,283 patients were analyzed to determine annual incidence and prevalence of the disease. Patients were treated at leprosy health centers in Juiz de Fora. The 1,283 patients included 375 cases reported prior to 1978, 534 new cases reported during period I (1978-1986), and 374 new cases reported during period II (1987-1995). Less than 10% of the patients from period I were treated with MDT, and some 90% had sulfone monotherapy from the National Sanitary Dermatology Division (DNDS). In contrast, approximately 90% of the patients from period II were treated with MDT, and less than 10% with the DNDS regimen. Leprosy classification was based on clinical presentation, bacilloscopy, Mitsuda test, and classic histopathology (MS, 1989) in both periods. Mitsuda test was used mainly to assist definition of indeterminate forms of leprosy. Until 1993, patients were considered cured after completion of treatment if clinical signs and bacilloscopy were both negative; otherwise they remained under observation for an additional period of 5 years (MB) or 2 years (PB). Statistical criteria for discharge were adopted in 1987. Patients absent from health units for a period of a year or more whose treatment was not completed were considered non-compliant and discharged by statistical criteria after completing 2 years (PB) or 5 years (MB) of dropout. Fixed-duration treatment was introduced in 1993.

Treatment efficacy was evaluated by the number of discharges resulting from cure and by comparing prevalence and incidence rates for the two study periods. In the second phase of the analysis, the case identification strategy, most frequent clinical presentation, age distribution, and source of infection were determined by analysis of randomly sampled medical charts. 314 files were selected in each of the two study periods, totaling 628 new case protocols.

Data were analyzed using EPI Info 6.03. We first did a descriptive statistical analysis for the two groups enrolled in this study. The results of phase one (Table 2) were compared by analysis of variance of the means using the non-parametric Kruskal-Wallis method. For the results in phase two (Figures 1-3), chi-squared statistics were used to analyze the data. The significance level was 5%.

Table 1

Characteristics of Period I and Period II.

	Period I	**Period II**
Time period	01/01/78 to 12/31/86	01/01/87 to 12/31/95
Main drugs and length of treatment	DNDS MB: Rfm + Dds (first 3 months) and Dds alone (through the remainder of 5 years) PB: Dds (2 years)	MDT MB: Rfm + Dds + Cfz (normally 24 months, up to 36 months) PB: Rfm + Dds (normally 6 months, up to 9 months)
Discharge based on statistical criteria	Not performed	Performed
Examination of contacts	Less frequent	More frequent
BCG vaccination[a]	Less frequent	More frequent
Professional training	Less frequent	More frequent

[a] BCG was introduced in 1989 for all MB contacts and in 1993 for all leprosy contacts.
Before 1989 it was only used for scar-negative contacts (usually children from 0 to 4 years of age).
Rfm = Rifampin; Dds = Dapsone; Cfz = Clofazimine; MB = Multibacillary Forms; PB = Paucibacillary Forms;
DNDS = National Sanitary Dermatology Division; MDT = Multidrug Therapy

Table 2

Number of admissions and discharges from leprosy register in Juiz de Fora in two periods.

Year	**Cases**[a]	**Admissions**[b]	**Discharges**[c]					**Population**[d]	**Incidence/ 100,000 inhab.**	**Prevalence/ 10,000 inhab.**
			Cure	Death	Change of resid.	Stat. Criteria	Total			
1978	375	49	0	0	0	0	0	293,000	17	14
1979	424	91	0	0	0	0	0	300,000	30	17
1980	515	66	1	0	2	0	3	307,525	21	19
1981	578	36	4	0	4	0	8	314,658	11	19
1982	606	45	20	1	3	0	24	321,789	14	19
1983	627	60	13	0	2	0	15	328,920	18	20
1984	672	95	4	0	10	0	14	336,051	28	22
1985	753	50	6	3	7	0	16	343,182	14	23
1986	787	42	1	4	14	0	19	350,313	12	22
Total		534	49	8	42	0	99			
1987	810	32	76	5	28	34	143	357,444	9	19
1988	699	47	75	9	15	7	96	364,575	13	17
1989	640	33	68	9	4	14	95	371,706	9	15
1990	578	55	77	4	7	29	117	378,834	14	14
1991	516	39	45	2	8	22	77	385,996	10	12
1992	478	53	61	7	6	42	116	393,127	13	10
1993	415	37	94	2	11	29	136	400,258	9	8
1994	316	55	82	2	4	19	107	407,389	13	6
1995	264	23	34	1	9	28	72	414,520	5	5
Total		374	612	41	92	224	959			

a – number of leprosy cases in active file at the end of previous year.
b – number of new cases recorded.
c – number of cases excluded from active file due to cure, death, change of residence, or statistical criteria.
d – estimated population for the year.

Results

The impact of MDT on the number of leprosy patients in Juiz de Fora

MDT was introduced in Juiz de Fora in 1987 and caused a reduction in treatment time. This change coincided with improvements in the leprosy surveillance system, including more frequent examination of contacts and professional training. In addition, a statistical criterion was introduced for patient removal from the register due to treatment non-compliance, and BCG vaccination was adopted in 1989 in an attempt to stimulate protective anti-mycobacterial responses in leprosy contacts (Table 1).

From 1978 to 1986 (period I), the number of new cases recorded in Juiz de Fora exceeded the number of discharges of patients on active file from the city health units, such that the total number of registered cases increased every year, peaking at 787 in 1986 (Table 2). Disease prevalence increased from 14.4 patients/10,000 inhabitants in 1978 to 22 patients/10,000 inhabitants in 1986. During this time, 534 new individuals were added to the register and only 99 were removed. Reasons for removal from the register were as follows: cure, 49.5%; change of residence, 42.4%, and death, 8%. In contrast, from 1987 to 1995 (period II), discharges (removal from the register) outnumbered new cases. There were a total of 810 cases in 1987, but the figure dropped to 264 by 1995. Accordingly, during period II, 959 discharges occurred. This was almost 10 times the figure for period I. A total of 63.8% of the patients were discharged due to cure, 23.3% based on statistical criteria, 9.6% because of change of residence, 4.3% due to death. The results suggest that the use of MDT improved the epidemiological control of the disease, reversing the flow of new cases and discharges, demonstrating a statistically significant improvement in the number of discharges due to cure ($p = 0.0003$), and reducing the overall disease prevalence from 19.5 cases/10,000 inhabitants in 1987 to 5.2 cases/10,000 inhabitants in 1995. Table 2 also shows that while the leprosy incidence rate in Juiz de Fora varied, it was lower during period II as compared to period I ($p = 0.0051$), suggesting that the incidence decreased after introduction of MDT, perhaps as a result of the decreased number of individuals infecting others.

Comparison of new case detection in period I *vs.* period II

Figure 1 shows the frequency of ways by which new leprosy cases were detected in Juiz de Fora in the two treatment periods. Patient self-referral for treatment at health units was the most frequent method of new case identification in period II (48.4%). This was clearly higher than patient self-referral during period I (11.1%). Likewise, the percentage of patients identified by health care professionals increased from 2.2% during period I to 26.8% during period II. Case identification through tests of previously identified patient contacts also became more prevalent in Juiz de Fora in period II (10.2%) as compared to period I (3.5%). In contrast, there was a reduction in the percentage of cases identified by mass screening (3.2% to 1.3%) as well as a reduction in the percentage of patients whose case identification mechanism was not determined during period II (13.4%) as compared to period I (79.9%). The overall distribution of case identification changed in a statistically significant manner ($\chi^2 = 300.27$, 4 df, $p<0.0001$) between the two periods.

Multibacillary forms of leprosy predominate over paucibacillary forms

It is well known that leprosy manifests as a spectrum of different clinical presentations. In our study, we observed that the multibacillary forms (lepromatous and dimorphous) predominated over paucibacillary forms (tuberculoid and indeterminate) in both study periods (Figure 2). A reduction in the percentage of all leprosy cases with the lepromatous clinical form (60.8% to 33.8%) from period I to period II was accompanied by an increase in dimorphous cases (1.9% to 38.5%). In contrast, the percentage of patients with tuberculoid leprosy did not show a significant variation, remaining at ≅19.5%. Patients with indeterminate leprosy represent less than 15% of the total number of patients, showing a drop from 14% to 11.8% from the first to second period. The overall distribution showed a statistically significant change from period I to period II ($\chi^2 = 133.37$, 3 df, $p<0.0001$).

The increased incidence of leprosy at extreme ages

Figure 3 shows that although leprosy was diagnosed mainly between 15 and 59 years of age, the percentage of patients 60 and over increased (from 7.5% to 12.5%) as did the per-

Figure 1

Leprosy case identification strategy in Juiz de Fora in the two periods.

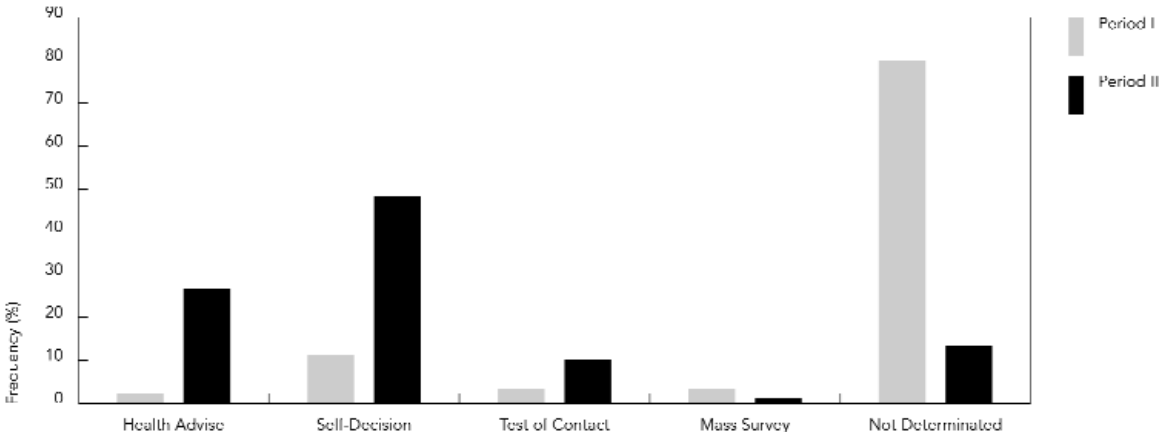


Figure 2

Clinical distribution of leprosy in the two periods.

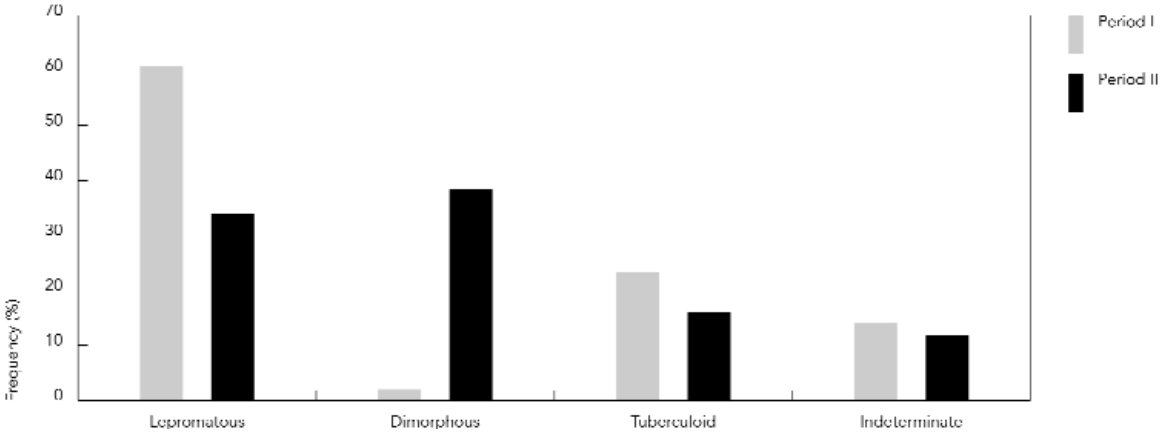
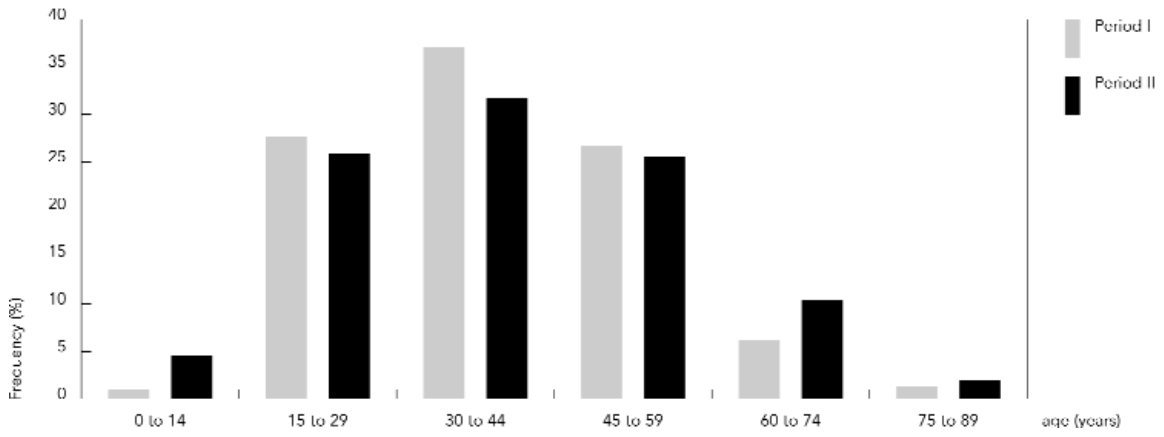


Figure 3

Age distribution of leprosy in the two periods.



centage of clinical presentations in patients below 15 years of age (1.0% to 4.6%). The overall change was significant ($\chi^2 = 12.52$, 5 df, $p = 0.0283$).

Discussion

The epidemiological features of leprosy were analyzed in Juiz de Fora, Brazil, focusing on the introduction of the MDT protocol and its impact on the epidemiological control of the disease. Our results demonstrate that use of MDT in Juiz de Fora beginning in 1986 caused a sharp decrease in overall disease prevalence as well as a significant increase in the number of discharges resulting from leprosy cure. These data suggest the efficacy of the MDT regimen for treatment of leprosy and confirm the prevalence studies described in other regions of Brazil (Nogueira et al., 1995; MS, 1998). Accordingly, recent data indicate that prevalence rates for leprosy in Juiz de Fora have continued to drop, with only 1.8 patients/10,000 inhabitants in 1996 and 1.6 patients/10,000 inhabitants in 1997 and 1998 (A. F. M. Pimentel, personal communication). This appears to be a continuation of the decreased incidence reported in this study between periods I and II. However, these findings are in contrast with the increased detection rates for new leprosy cases observed throughout Brazil during the period from 1986 to 1997 (MS, 1998). This disparity could be explained by large differences between leprosy incidence in different regions of Brazil as well as differential employment of MDT regimens. However, our data are consistent with the results described by others using retrospective analysis of data on the occurrence of leprosy worldwide (Myint & Htoon, 1996; Meima et al., 1997).

We are aware that the reduction in treatment time and implementation of statistical criteria for being discharged from the active file (both adopted after 1986) may have some influence on the interpretation of the success of MDT. Increased BCG vaccine coverage could also have affected our data by lowering the incidence of the lepromatous form, since it has been demonstrated that BCG confers protection against leprosy and is able to decrease the proportion of MB forms (Rodrigues et al., 1992; Bertolli et al., 1997). Still, we believe that implementation of the MDT program in Juiz de Fora has produced major changes in patient treatment and cure. Since these changes were accompanied by improvements in both surveillance and health services' availability and quality, it is highly unlikely that the decrease in incidence and prevalence are merely the result of changes in the definition of cure or vaccine coverage.

The increase in frequency of patient self-referral for treatment of leprosy at health units in Juiz de Fora suggests that after the initiation of the MDT program there was an improvement

in the population's knowledge of the early signs and symptoms of the disease and the availability of medical care. In addition, improved recognition of the disease by health professionals and increased surveillance of patient contacts resulted in a higher percentage of case identification through referral by health professionals. The reduction in the percentage of patients identified by mass screening confirms other studies, according to which this high-cost strategy for detecting new cases has been discontinued (Theuvenet et al., 1994).

As expected, the percentage of patients who acquired the disease through household contacts (≅24%) was higher than for those who acquired the disease by other known sources (≅7%) in both periods. The majority of patients (≅68% in both periods) could not identify the source of infection. The close association of the patients with asymptomatic leprosy carriers living in endemic areas of disease may explain the occurrence of new cases of leprosy for which the source of infection is not known (Van Beers et al., 1994). This possibility is enhanced by the long viability of *Mycobacterium leprae* outside the human body (Desikan & Sreevatsa, 1995). These data implicate a role of genetic features and prolonged contact with asymptomatic carriers in the spread of disease (Kyriakis et al., 1994; Mehra et al., 1995; Abel et al., 1998). However, there is still little information on the main source of infection in these situations.

The multibacillary forms of leprosy predominated during both periods, but the frequency of dimorphous and lepromatous forms differed. Such variation may be explained by changes in the evaluation criteria for clinical presentations and by improved diagnostic accuracy. However, most dimorphous cases in period II are, in fact, skin-smear-negative patients (83.6%), as compared to the smear-positive patients who were predominant among the lepromatous patients in period II (73.6%), showing a highly significant difference (χ^2 = 61.18, 1 df, p<0.0001). Hence, we cannot exclude the possibility that the described shift in dimorphous frequency and the high detection rate for MB leprosy may, to a certain degree, reflect a conservative behavior in which clinicians prefer to choose longer treatment for leprosy patients (Martelli et al., 1995). The incidence of leprosy in females (44.5%) was lower than in males (55.5%), but the difference was not statistically significant (χ^2 = 1.17, df = 1, p = 0.2783); interestingly, a higher percentage of MB leprosy was observed in males than females (73.7% *versus* 59.6%) during both periods (χ^2 = 13.99, 1 df, p<0.0002). These findings reinforce the concept that immune responses against *M. leprae* are stronger in females than in males (Olrich et al., 1993).

Although most leprosy cases occur between 15 and 60 years of age, the current data suggest a broader age distribution in this population. An increased frequency of leprosy in patients 60 years of age or older was observed, similar to reports by others (Smith & Richardus, 1993). The percentage of children under 15 with the disease changed from low to moderate according to WHO criteria. The same results were also described elsewhere (MS, 1998) and are considered an indicator of a higher rate of disease occurrence, but they may also be associated in some way with improvements in case detection.

During period II, 224 patients were discharged by statistical criteria and were thus lost to follow-up along with 284 asymptomatic leprosy carriers who have a significant risk of developing the disease in the future. Nevertheless, the use of MDT as a new treatment protocol for leprosy patients reduced the non-compliance rate in Juiz de Fora from 90% in 1986 to 56% in 1995. This non-compliance rate is still considered high and might jeopardize the leprosy control program, since the lack of completed patient treatment and contact follow-up could lead to development of resistant bacilli.

The MDT program shows good prospects for the cure of leprosy and its elimination as a public health problem (WHO, 1994). However, we must not forget that the control and eradication of the disease hinge on different collective efforts that can interfere with the spread and evolution of the disease. Such efforts are not restricted to the use of drugs against *M. leprae* but can also employ integrated nutritional programs, BCG coverage, school curricula, and sanitary conditions. These factors may also influence the efficacy of patients' immune response, clinical presentation, and treatment results.

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