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THE IMPACT OF MULTIDRUG THERAPY ON THE EPIDEMIOLOGIC PATTERN OF LEPROSY IN JUIZ DE FORA, BRASIL.

Running Title: Impact of MDT on Leprosy Prevalence

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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. An evaluation of 1283 medical charts of leprosy patients was undertaken, according to the therapeutic schedule used in two different periods, by using the Epi Info 6.03 program. Since the introduction of MDT in 1987, the prevalence of leprosy decreased from 22 patients/10,000 inhabitants to 5.2 patients/10,000 inhabitants in 1995. The decreasing prevalence appears to be related to drug efficacy rather than decreased infection identification as both self-initiated and health care professional referral sought treatment increased markedly from period I (1978-1986) to period II (1987-1995). For both periods, multibacillary leprosy was the most frequent clinical form of the disease (±76%) and the main known risk factor for infection was contact in the home. Although leprosy is predominantly manifested in adults, an increase in the percentage of very old and very young patients was observed in period II. In conclusion, the results indicate that the MDT program has been effective in combating leprosy and has increased awareness of the disease. Elements that might impair the success of the MDT leprosy control program are also discussed.

Keywords: Leprosy, Multidrug therapy, Epidemiology, Prevalence
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 1283 prontuários de pacientes com hanseníase, de acordo com o esquema terapêutico adotado em 2 diferentes períodos, utilizando o programa EPI-INFO 6.03. Desde a introdução da PQT em 1987, a prevalência da hanseníase caiu de 22 pacientes/10.000 habitantes para 5,2 pacientes/10.000 habitantes em 1995. A diminuição da prevalência está mais relacionada à eficácia das drogas usadas do que a uma queda na identificação da infecção, já que tanto a procura espontânea bem como os encaminhamentos feitos por profissionais de saúde aumentaram significativamente do período I (1978-1986) para o período II (1987-1995). Em ambos os períodos, a forma clínica mais frequente foi a multibacilar (±76%), e o contato intradomiciliar foi o maior fator de risco conhecido associado à infecção. Embora a hanseníase manifeste predominantemente em adultos, um aumento na porcentagem de pacientes muito velhos ou muito novos foi observado no período II. Concluindo, os resultados indicam que o esquema PQT tem sido eficaz no combate à hanseníase, e tem aumentado a conscientização e o conhecimento da doença. Fatores que podem comprometer o sucesso da PQT também são discutidos.

Palavras-chave: Hanseníase, Poliquimioterapia, Epidemiologia, Prevalência.
1) **INTRODUCTION**

Leprosy is a chronic infectious disease that represents a major public health problem affecting about 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 disease afflicting humans, only the advent of sulfones in the 1940's provided the possibility for its treatment and cure. However, the outcomes experienced with the use of sulfones were not satisfactory. Dapsone failed to prevent the growth of resistant bacillus (Dharomendra 1986) and new potent drugs like clofazimine (Browne & Hogerzeil 1962) and rifampicin (Levy et al. 1976; Opromolla 1963) could not control the dissemination of the disease as monotherapeutic agents. In 1981, World Health Organization (WHO) began to recommend 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 multibacillary form and from 2 years to 6 months for the paucibacillary form. MDT was introduced in Brasil in 1986 and it was authorized for leprosy treatment in 1992.

Based on the efficacy of MDT for leprosy, WHO has targeted elimination of the disease as a world-wide public health problem by the year 2000. To do so, it has enrolled the authorities of countries with high rates of disease. Brazil currently has the second highest prevalence and incidence of leprosy in the world. The Brazilian government, through its Health State Offices, has been working to reduce the prevalence of the disease to less than 1 case per 10,000 inhabitants, which is considered a low rate by WHO.
Juiz de Fora, a city with a population of 414,520 inhabitants (population estimate for 1995), has many patients with leprosy. However, the epidemiologic pattern of the disease in the city has not been described. This article analyses the main characteristics of leprosy in Juiz de Fora and investigates the impact of MDT on the epidemiologic pattern of the disease.
2) PATIENTS AND METHODS

Juiz de Fora is the home of a regional health directorate of 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 that care for patients with leprosy: Dr. Antonio Carlos Pereira Filho - Dermatology Sector and Universitary Hospital. We studied the epidemiologic patterns of patients with leprosy over two defined periods, differing in their use of MDT:

Period I: from 01/01/78 to 12/31/86. Less than 10% of the patients were treated with MDT and about 90% of the patients had sulfone monotherapeutic treatment from the National Sanitary Dermatology Division (DNDS).

Period II: from 01/01/1987 to 12/31/95. Approximately 90% of the patients were treated with MDT and less than 10% with the DNDS schedule.

Medical charts of 1283 patients treated at leprosy health centers in Juiz de Fora were analysed to determine the incidence and the prevalence of disease. Efficacy of the therapy used was evaluated by the number of discharges resulting from cure of the disease. In addition, the case identification strategy, the infection source, the most frequent clinical presentation and the age distribution were determined by analysis of 314 medical charts of patients from each one of the two periods studied.

The data were analysed using the computer program EPI Info 6.03. First we did a descriptive statistical analysis for the two groups enrolled in this study. The results were compared by analysis of variance of the means using the non-parametric Kruskal-Wallis method. The significance level was 5%.
3) RESULTS

3.1) THE IMPACT OF MDT ON THE NUMBER OF PATIENTS WITH LEPROSY IN JUIZ DE FORA.

From 1978 to 1986 (period I), the number of new cases registered in Juiz de Fora exceeded the number of discharges of patients on active file from the city health units, so that the total number of registered cases increased every year peaking at 787 in 1986 (table 1). The 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. The reasons for removal from registry were 49.5% for leprosy cure, 42.4% for locality transfer and 8% by patient death. In contrast, from 1987 to 1995 (period II) the number of discharges (removal from the registry) overcame the number of additions. The total number of cases in 1987 was 810 but decreased to 264 by 1995. Accordingly, during period II, 959 discharges occurred. This was almost 10 times the number of period I. 63.8% of the patients were discharged due to cure, 23.3% by statistical criteria, 9.6% because of locality transfer and 4.3% by patient death. Thus, the use of MDT improved the epidemiologic control of the disease as it reverted the flow of new registrations and discharges. It demonstrated a statistical significant improvement in the number of discharges as a result of cure (p=0.0063) and it reduced the overall disease prevalence from 19.5 cases/10,000 inhabitants in 1987 to 5.2 cases/10,000 inhabitants in 1995. Table I also shows that the incidence rate of leprosy in Juiz de Fora varied but showed lower incidence during period II compared to period I (P<0.05), suggesting that the incidence of leprosy reduced after introduction of MDT, perhaps as a result of the decreased number of individuals infectious to others.
3.2) COMPARISON OF NEW CASE IDENTIFICATION IN PERIOD I VS. PERIOD II.

Figure 1 shows the frequency of how new cases of leprosy were identified in Juiz de Fora in the two treatment periods. Patient initiated pursuit of treatment at health units was the most frequent method of new cases identification in Period II (44%). This was significantly higher than the patient initiated treatment sought during period I (6%, p<0.05). Similarly, the percentage of patients identified by health care professionals increased from 1% during Period I to 28.4% during Period II. Case identification through tests of previously identified patient contacts also became more prevalent in Juiz de Fora in Period II (10.3%) compared with Period I (3%, p<0.05). In contrast, there was a reduction in the percentage of case identified by mass survey (6.6% to 1.9%, p<0.05) as well as a reduction in the percentage of patients whose case identification mechanism was not determined during Period II (16.3%) compared with Period I (83.8%, p<0.05).

3.3) THE MAIN SOURCE OF INFECTION DESCRIBED IS HOME CONTACT

The value of test of contacts for early diagnosis and control of leprosy is grounded on the high incidence of the disease in family members of current patients. Accordingly, this study verified that the percentage of patients who acquired the disease by home contact (±26%) was higher than those who acquired the disease by other known source (±6%), in both periods. The majority of patients (±68%) could not identify the source of infection (Figure 2).
3.4) THE MULTIBACILLAR FORMS OF LEPROSY PREDOMINATE OVER THE PAUCIBACILLAR FORMS.

It is well known that leprosy manifests as a spectrum of different clinical forms. In our study, it was observed that the multibacillar forms (lepromatous and dimorphous) predominate over paucibacillar forms (tuberculoid and indeterminate) in both periods studied (figure 3). A reduction of lepromatous leprosy frequency (70% to 38%) from Period I to Period II was accompanied by a raise of dimorphous leprosy cases (2% to 43%). In contrast, the percentage of patients who had tuberculoid leprosy did not show a significant variation, remaining at ≈14.5%. Patients with indeterminate leprosy represent less than 10% of the total number of patients, showing a drop from 8.6% to 4.3% between the periods studied.

3.5) THE INCIDENCE OF LEPROSY INCREASED AT EXTREME AGES

Figure 4 shows that although leprosy was diagnosed mainly in adults (15 to 60 years of age), the percentage of patients over 60 with clinical presentation of the disease increased significantly (4.5% to 11.2%, p<0.05) as did the percentage of clinical presentations in patients below 15 years of age also raised (2.5% to 6%, p<0.05).
4) DISCUSSION

The epidemiologic features of leprosy were analysed in Juiz de Fora, Brazil, focusing on the impact of the introduction of the MDT protocol on the epidemiologic control of the disease. Our results show that the use of MDT in Juiz de Fora since 1986 caused a sharp decrease in disease prevalence as well as a significant increase in the number of discharges resulting from leprosy cure. These data prove the efficacy of MDT schedule for treatment of leprosy and confirm the results described in other regions of Brazil (Nogueira et al. 1995). In addition, more recent data indicate that prevalence rates of leprosy in Juiz de Fora were reduced to 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). Thus, the implementation of MDT in Juiz de Fora has brought about major changes in patients treatment and stresses the effectiveness of the WHO-recommended MDT schedule as a potent tool for national control programs designed to eliminate leprosy as a public health problem (WHO 1994).

As expected, the percentage of patients who acquired the disease through contact with another patient at home is higher than those who got it outside the home contacts throughout the study period. Similar observations have been made by other authors (Kyriakis et al. 1994). Recently, it has been demonstrated that a higher susceptibility to leprosy might be associated with certain MHC molecules in patients, such as the DR2 e DQw1 subtypes (Todd et al. 1990; Mehra et al. 1995). The spread of the disease by indirect contacts and the occurrence of new cases of leprosy for which the source of infection is not known might be explained by the close association of the patients with asymptomatic leprosy carriers living in endemic areas of disease. This possibility is enhanced by the long viability of M. leprae outside the human body (Van Beers et al. 1995). These data implicate a role of genetic features and prolonged
contact with assymptomatic carriers in the spread of disease. However, there is still very little evidence of the main sources of infection in these situations.

The increase in frequency of patients seeking treatment for care of leprosy at health units in Juiz de Fora suggests that following 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. On the other hand, improved recognition of the disease by health professionals increased surveillance of patient contacts and resulted in a higher percentage of case discovery by professional reference. The reduction on the percentage of patients identified by mass survey confirms other studies which showed that this high cost new case find strategy has been discontinued (Theuvenet et al. 1994).

Although the multibacillary forms predominated during both periods, the frequency of dimorphous leprosy and lepromatous leprosy differed. Such variation can be explained by changes in the evaluation criteria of clinical presentations and by improved diagnostic accuracy. The incidence of leprosy in females (36%) was lower than in males (64%–data not showed). These percentage are consistent with those found in most of Latin America and reinforce the concept that immunologic responses against *M. leprae* is stronger in females than in males (Olrich *et al.* 1993).

An increased frequency of leprosy in patients 60 years of age or older was observed, similar to the results found by Smith, T.C. and Richardus, J.H. (1993). The percentage of children under 15 with the disease changed from low to moderate according to WHO criteria. Although leprosy predominates between 15 to 60 years of age, the current data suggest a larger age distribution of leprosy in this population.
Patients absent from health units for a period of a year or more whose treatment was not completed are considered as non-compliant and are discharged by statistical criteria. Two-hundred and twenty four patients were discharged by statistical criteria and therefore were lost to follow-up along with 284 assymptomatic leprosy carriers who have a significant risk of disease development in the future. Nevertheless, the use of MDT as a new treatment protocol for patients with leprosy reduced the non-compliance rate in Juiz de Fora from 90% in 1986 to 56% in 1995 (data not shown). These non-compliance rates are still considered high and might jeopardize the leprosy control program as the lack of completed patient treatment and contact follow-up could lead to development of resistent bacilli. Another potential problem is the relapse rate observed in leprosy patients who have completed treatment, especially those with multibacillary leprosy. These presentations need further investigation and might be related to: (i) irregular or inappropriate treatment, (ii) reinfection, (iii) bacterial resistance and/or (iv) incorrect diagnosis of recrudescence leprosy (Daumerie & Panniker 1995).

The MDT program shows good prospect for the cure of leprosy and its elimination as public health problem. However, it cannot be forgotten that the control and the eradication of the disease rely 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, educational curricula and sanitary conditions. These factors may also influence the efficacy patient's immunologic response, the clinical presentation and the therapeutic results.
Acknowledgments: Dr. Marcio José Martins Alves for his suggestions and help on the statistical analysis of the data. Dr. Evan Secor for critical review of the manuscript. This work was supported by grants from Conselho Nacional de Pesquisa (CNPq) and Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG).
5) REFERENCES:


Table 1 – Number of admissions and discharges from file of leprosy in Juiz de Fora in two different periods. 1283 medical charts of patients treated in the city health centers were analyzed. Period I: from 01/01/78 to 12/31/86 (10% MDT treatment, black bars); Period II: from 01/01/87 to 12/31/95 (90% MDT treatment, grey bars).

Fig. 1 – Case Identification strategy of leprosy in Juiz de Fora in the two different periods.

Fig. 2 – Sources of infection in the two different periods.

Fig. 3 – Clinical distribution of leprosy in the two different periods.

Fig. 4 – Age distribution of leprosy in the two different periods.
Table 1 - Number of Admissions and discharges from file of leprosy in the city of Juiz de Fora

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of cases</th>
<th>Admission</th>
<th>Discharges</th>
<th>Population</th>
<th>Incidence</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Cure</td>
<td>Death</td>
<td>Trans</td>
<td>A. Est.</td>
<td>Total</td>
</tr>
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<td>49</td>
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<td>0</td>
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<td>1981</td>
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<td>36</td>
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<td>4</td>
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<tr>
<td>TOTAL</td>
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<td>49</td>
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<td>42</td>
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</tr>
<tr>
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<td>810</td>
<td>32</td>
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<td>5</td>
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<td>34</td>
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<tr>
<td>1988</td>
<td>699</td>
<td>47</td>
<td>75</td>
<td>9</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>1989</td>
<td>640</td>
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<td>9</td>
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<tr>
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<td>1</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>374</td>
<td>612</td>
<td>41</td>
<td>92</td>
<td>224</td>
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</table>
The chart shows the frequency of contact and ignored interactions during Period I and Period II. The data is represented as follows:

<table>
<thead>
<tr>
<th></th>
<th>Period I</th>
<th>Period II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home Contact</td>
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<td>31</td>
</tr>
<tr>
<td>Indirect Contact</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Ignored</td>
<td>72</td>
<td>64</td>
</tr>
</tbody>
</table>

**FIG 2**
The graph compares the frequency (%) of Lepromatous, Dimorphous, Tuberculoid, Indeterminated, and No Register cases between Period I and Period II.

### Frequency Comparison

<table>
<thead>
<tr>
<th>Type</th>
<th>Period I</th>
<th>Period II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepromatous</td>
<td>70</td>
<td>38</td>
</tr>
<tr>
<td>Dimorphous</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>Tuberculoid</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>No Register</td>
<td>4</td>
<td>1</td>
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</tbody>
</table>