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CHEMOPROPHYLAXIS TO CONTROL LEPROSY AND THE PERSPECTIVE OF ITS IMPLEMENTATION IN BRAZIL: A PRIMER FOR NON-EPIDEMIOLOGISTS

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SUMMARY

The occurrence of leprosy has decreased in the world but the perspective of its elimination has been questioned. A proposed control measure is the use of post-exposure chemoprophylaxis (PEP) among contacts, but there are still questions about its operational aspects. In this text we discuss the evidence available in literature, explain some concepts in epidemiology commonly used in the research on this topic, analyze the appropriateness of implementing PEP in the context of Brazil, and answer a set of key questions. We argue some points: (1) the number of contacts that need to receive PEP in order to prevent one additional case of disease is not easy to be generalized from the studies; (2) areas covered by the family health program are the priority settings where PEP could be implemented; (3) there is no need for a second dose; (4) risk for drug resistance seems to be very small; (5) the usefulness of a serological test to identify a higher risk group of individuals among contacts is questionable. Given that, we recommend that, if it is decided to start PEP in Brazil, it should start on a small scale and, as new evidence can be generated in terms of feasibility, sustainability and impact, it could move up a scale, or not, for a wider intervention.

KEYWORDS: Contact tracing; Leprosy; Prevention and control; Chemoprophylaxis.

INTRODUCTION

The occurrence of leprosy has decreased in the world, but more than 200,000 cases are still registered every year[52] and the perspective of its elimination is being questioned[18,19]. Most of the control strategies rely on earlier case detection, treatment with multidrug therapy (MDT) and contact tracing. In Brazil, 32,945 new cases were reported in 2012[4] and the Brazilian Ministry of Health officially recommended physical examination of all household contacts to guarantee early detection of new cases, and BCG vaccination.

Another proposed control measure is the use of post-exposure chemoprophylaxis (PEP) among contacts of leprosy cases. PEP has been studied in randomized controlled trials (RCT) and observational studies since 1960s; the results have been summarized in two systematic literature reviews (SLR)[36,41] and debated in the literature[32,33,42,51]. However, as far as we know, neither the World Health Organization nor the leprosy national programs have included PEP in their list of official recommendations. Given that protection has already been demonstrated, the main pending questions pertain to the operational aspects of implementing the PEP strategy[43] and its real value in the control of leprosy.

In this text, we discuss the appropriateness of implementing PEP in Brazil by providing answers to some frequently asked questions by health professionals, aiming to reach a wide audience and a comprehensive bibliography on the topic.

What do the epidemiologic studies tell us about PEP protection against leprosy?

First, we need to clarify some concepts. In a RCT, the risk of leprosy in contacts who receive PEP is compared to contacts who do not receive the intervention (control). In a typical RCT, the intervention is done under ideal conditions and the effect is called therefore "efficacy"; if the study is carried out under routine conditions, the effect is called "effectiveness". When an RCT reports that PEP had 50% protection, this means that the risk of developing the disease in contacts that received PEP was 50% lower than in contacts who did not receive PEP. But what would be the reduction in the entire population? If 50% of cases in the entire population came from individuals known to be contacts of leprosy cases, and given that PEP administered to contacts provides a reduction of 50% of cases among contacts, the reduction in the entire population would be 0.5 x 0.5 = 0.25 or 25%, considering that all contacts received PEP. This is called "population impact" of the chemoprophylaxis program. The population impact measures the reduction of leprosy risk in the entire population when PEP is done in contacts. These measures correspond to the terminology used in vaccine studies[17].

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It is worth saying that the RCTs on PEP were not conducted reproducing routine conditions of the programs where the studies were conducted and this has implications for the generalization of the results. It is not clear, for example, what would be the reduction of the risk of leprosy in the entire population if PEP were used in contacts in Brazil, due to what would be the proportion of contacts that would receive PEP and the high coverage rate of BCG, given that BCG also confers protection against leprosy[23].

What was the PEP protection measured in the RCTs?

In the six RCTs that have been published so far, PEP was done with several doses of acedapsone (three studies), dapsone (two studies), and one single dose of rifampicin (one study). The protection in contacts varied from 35 to 57% (all of them had statistically significant results)[36,41]. It seems that there was another unpublished study in Thailand that found a protection of 50%, which was not statistically significant[43], but it is not possible to have an appraisal of this evidence.

Two additional observations are particularly important from the last trial, the one that used a single dose of rifampicin in Bangladesh. Firstly, the observed protection was higher (80%, 95% C.I.: 50-92%) among those contacts who had been vaccinated with BCG in comparison to those not vaccinated (58%, 95% C.I.: 30-74%)[40]. This finding can be important because in many countries, including Brazil, BCG coverage rates are high and thus the protection conferred by PEP could eventually reach higher levels than those reported in trials. Secondly, the observed protection was higher among contacts who were not closely related to the index cases in comparison to those who were closely related[24]. This is potentially important as it could suggest that the implementation of PEP should also include other contacts aside from household members.

However, these findings should be interpreted with caution, as they correspond to "subgroup analyzes": the estimation of the effect of an intervention separately for two or more groups of the study population. For example, in the comparison of the PEP effect separately for those with BCG and for those without BCG shown above, there is an overlap in the confidence intervals and therefore it cannot be ruled out that this difference was not obtained by chance[5,21]. A study is currently being carried out for further clarification of these different protection effects[38].

Can PEP implemented only among contacts reduce the risk of disease in the entire population?

PEP is mainly recommended to a fraction of the population: those who are in contact with leprosy cases, and this fraction cannot be modified by an intervention. This means that the population impact will depend on two factors. Firstly, the number of cases that are directly derived from known/identifiable contacts. Secondly, on whether it is possible that PEP given to contacts can also reduce the risk among other individuals who do not receive PEP (this is called indirect effect) by removing the sources of infection and therefore reducing disease transmission. Unfortunately, there is no evidence so far that PEP for leprosy produces the indirect effect[14]. This means that any reduction in the entire population is due to reduction of cases among contacts.

Should chemoprophylaxis also be given to the general population rather than only to contacts?

The fact that there is no indirect effect could suggest that chemoprophylaxis should be done also in the entire population. In one RCT, all individuals in an endemic area were considered contacts and chemoprophylaxis was administered to all individuals below the age of 25[49]. One controlled but not randomized trial[1] and some before-after observational studies[8,11] have been also carried out in the general population with observed protection of > 75%. However, these observational studies are more susceptible to bias and the use of chemoprophylaxis in the general population poses many challenges. Firstly, the number of individuals receiving the drug would be high. Secondly, it would probably be necessary to repeat the chemoprophylaxis for as long as new leprosy cases occur. Operationally, this seems to be very difficult and probably not desirable. What could perhaps be reasonable is to use chemoprophylaxis in a particular small community with a high incidence of leprosy. But again, it is hard to define how small this community should be, and what would be the cut-off incidence that should trigger the intervention. It is likely that these questions should be discussed in each context.

Another issue is that the proportion of cases that comes from contacts seems to vary as a function of the overall occurrence of the disease: it seems to be higher where the occurrence of leprosy is low and smaller where the occurrence is high[37]. This implies that the population impact possibly varies in different settings, and thus it is not easily generalizable. But given that the occurrence of leprosy has decreased in Brazil, it is possible that the introduction of PEP will produce a higher reduction of cases in the entire population as a high proportion of cases acquires infection from contacts.

For how long does the protection conferred by PEP among contacts last?

Among contacts who receive PEP, there are those who have already been infected by the leprosy bacilli the moment they receive PEP and those who have not been infected. Let us call them groups 1 and 2, respectively. PEP acts exclusively among group 1 contacts, but has no effect on group 2, even if they have the possibility of becoming infected afterwards. When a study compares contacts that do and do not receive PEP, the initial reduction among those who receive is due to the protection conferred to group 1. But, given time and continual exposure, new cases of infections will happen and disease will continue to rise, particularly from those in group 2.

Therefore, it is expected that the difference in the risk of leprosy between those who have and have not received PEP will tend to decrease over the course of time[35] as it was observed in the last RCT that used one single dose of rifampicin[24], where a reduction of protection was observed after 2-3 years. This is not a decrease in protection, in a strict sense, as those in group 1 who have received PEP still have a reduced risk of leprosy as compared to group 1 contacts that have not received it.

However, it is important to emphasize that the risk of developing the disease once one has been infected tends to decrease in all contacts over time, having received PEP or not. This happens for two reasons. Firstly, most cases among contacts are paucibacillary (PB), have shorter

incubation period and thus infection occur sooner after exposure to the source. Secondly, transmission from the index cases to their contacts decreases gradually[12,47] after they initiate MDT.

Does PEP induce drug resistance?

The use of rifampicin in contacts raises the fear of increasing drug resistance, as PEP would use a single dose of rifampicin for dozens of thousands of individuals. However, despite evidence of drug resistance to leprosy bacilli, it is currently rare[7,50] and mostly confined to relapsed MB patients. Whether or not the widespread use of single antibiotics given on a single dose would increase the frequency of drug resistance is not currently known. It is possible to speculate that this is unlikely to happen, as it would only be a single dose given to asymptomatic individuals with possibly few viable bacilli instead of multiple doses given on a regular basis for months. But, in any case, this possibility strengthens the need for an effective drug resistance monitoring.

Should a second dose of PEP be given?

Some could argue that if protection wanes over time, a second dose should be repeated after two to three years in order to further decrease the risk of disease. However, it seems that most cases of leprosy among contacts are detected in the first two to three years after the detection of the index cases. This information is available in some prospective studies of contacts (Table 1). It was also described in a cohort study performed in Brazil[20,39]. Because of this fact, as compared to the first dose of PEP, each subsequent dose will prevent less and less cases from occurring. Therefore, it is possible that repeated PEP doses over time are unnecessary.

The case for a broader contact definition

The greater the proportion of cases arising from contacts, the greater the impact of PEP in the entire population. In a study in Indonesia, 79% of cases were from contacts including neighbour and social contacts[46]. Therefore, one solution to increase the impact on the population would be to broaden the contact definition. However, this would obviously increase costs and logistic efforts to find such contacts, and to convince them of the need to receive PEP. A broader definition was used in the last trial[24], but it is unclear whether it would be feasible to use the same wide definition under routine conditions.

Can BCG and rifampicin be given at the same moment to contacts?

In Brazil, according to the National Leprosy Program recommendations, BCG vaccine should be administered to those in contact with leprosy cases. In order to prevent the bactericidal activity of rifampicin from interfering with the immunization conferred by BCG (a live vaccine that dies with rifampicin use), it seems reasonable that PEP and BCG should not be given together. In an ongoing study, BCG

Table 1
Percentage of leprosy cases detected during follow-up in different longitudinal studies with contacts of leprosy cases

Study: Author, year of first publication, references	Study[1]	Total duration of follow-up	Percentage of cases per follow-up period in the control group
Moet, 2008[14,24]	RCT for chemoprophylaxis	5-6 years	Total: 108 1-2 years: 67 (62.0%) 3-4 years: 24 (22.2%) 5-6 years: 17 (15.7%)
Neelan, 1983[25]	RCT for chemoprophylaxis	Up to 180 weeks (~3.4 years)	Total: 42 Up to 90 weeks: 37 (88%)
Noordeen, 1976 [29,31]	RCT for chemoprophylaxis	Contacts of "non-lepromatous cases" = 3.5 years (185 weeks)	Total: 109 Up to 119 weeks (~ 2.2 years): 84 (77%)
		Contacts of lepromatous cases = 6 years (318 weeks)	Total: 38 Up to 150 weeks (~ 2.8 years): 34 (89%)
Dharmendra, 1965 [9,10,28,30]	RCT for chemoprophylaxis	3rd report up to 299 weeks (~ 5.6 years) (Last report up to 8 ½ years but with small cases of follow-up)	Total with 299 weeks: 48 Up to 149 weeks (~2.8 years): 39 (81%)
Stanley, 1981[45]	RCT for BCG in contacts	8 years	Total: 192 cases[2] Separately for survey and mean years for entry: 1st (mean 1.9 years): 103 (54%) 2nd (mean 3.3 years): 51 (27%) 3rd (mean 5.7 years): 27 (14%) 4th (mean 8.0 years): 11 (6%)

Notes: [1]RCT randomised control trial; [2]as in table 6 of the reference.

and PEP are being administered two months apart[38]. In Brazil, BCG is given to contacts and thus a clear recommendation should be made on administration intervals under routine situations. It is not known whether or not this gap would have implications for the follow-up of contacts.

Should a test be implemented to detect contacts that are exposed to a higher risk?

Based on the results of some studies, it has been suggested that programs should use a serological test to identify, among contacts, an even higher risk group of individuals that would be followed under a closer surveillance[12,13].

However, these results should be interpreted very carefully. Despite the fact that individuals who are positive to such tests have been shown to have a higher risk of getting the disease in comparison to those who are negative, it seems that the majority of new cases still arise from those who are negative, so surveillance would still be necessary for all contacts regardless of test results. Therefore, the real utility of implementing such tests in the routine of leprosy control activities is still to be demonstrated.

Let us consider an example of a study on this regard performed in Brazil[13]. In this study, 2,135 contacts had a serological test (PGL-1) and 16% were found to be positive (n = 342). After a follow-up of several years, 60 new cases were detected and the authors estimated that those with a positive test had a chance 3.2 times more than those with a negative test. However, the majority of cases occurred among negative contacts: 6**8**% (41/60) were negative and 3**2**% (19/60) were positive. In contrast, it was also observed that 90% (54/60) of the cases were from 1,570 contacts of index cases that were multibacillary (MB). If the justification for serology is to perform a close monitoring in a subgroup responsible for the majority of cases, it seems that obtaining the mere information of the clinical form of the index cases would be more useful, unless, someone could argue, maybe rightly, that it is easier to have a closer monitoring of 342 rather than of 1,570 individuals. In another study in the Philippines, multiple serological tests were performed to identify contacts at higher risks[12], with 559 contacts and 27 new cases diagnosed (10 MB and 17 PB). The risk of becoming a case for those who were positive was 7.15 higher than for those who were negative. But again, among the 27 new cases, only a minority (n = 7) were positive in the first test (25.9%), other seven seroconverted during follow-up, and 13 remained negative throughout follow-up. In this study, it seems that performing just one test to identify contacts that have a higher risk of becoming a case was not a good initiative, as these tests only predicted a minority of cases. Multiple tests would therefore need to be performed over time, increasing costs and logistics.

There is evidence supporting the fact that MB cases are the main source of infection, and so a close monitoring of their positive contacts could help to break the chain of transmission[12]. However, in the Brazilian study[13], out of the six new MB cases that were detected, four had been positive for the serological test; in the study in the Philippines[12], among 10 new MB cases, only three had been positive at the first exam. Indeed, it seems that the test is capable of identifying a subgroup in which most MB cases arise, but not all of them. Whether or not this could help to break the chain of leprosy transmission is yet to be demonstrated.

From an individual perspective, it could be desirable to determine through a simple serological test whether or not one has a higher risk of becoming a case. However, from the perspective of a control program, it should be considered whether or not this initiative actually contributes to decreasing the incidence of leprosy, to identifying most of those that would become new cases of leprosy (irrespective of them being a PB or an MB cases), or most new MB cases. The introduction of a test capable of identifying only a minority of the total cases and not even all MB cases will possibly not make much difference in practice, because contacts tested positive, negative and untested should still be ultimately monitored.

New field-friendly assays testing *M. leprae*-specific T cell responses seem to be more promising[3,16]. However, longitudinal studies are still needed to assess the accuracy in predicting who, among those who are healthy household contacts, has a higher risk of developing clinical leprosy.

Whatever the diagnostic test used, the whole strategy combining testing plus close monitoring should also be evaluated on the basis of its feasibility and costs, the compliance of positive contacts to the closer monitoring procedures, some quantification of how much earlier cases arising from positive contacts monitored closely would be detected in comparison to those followed under the routine surveillance; as well as the proportion of the total and MB cases arising from positive contacts.

Number needed to treat (NNT)

The NNT is the number of people that need to be treated (or need to use PEP) in order to prevent an additional case of disease[2]. If NNT is high, the intervention will possibly not be feasible and/or it will be too expensive. When the risk of leprosy is low in a population, more contacts have to receive chemoprophylaxis to prevent a new case, and vice versa.

NNT has been estimated in several PEP studies. However, it is important to emphasize that the interpretation of NNT should be done very carefully[22,44] as it depends highly on the absolute baseline risk and for how long NNT is measured. For example, if in a hypothetical scenario the risk of leprosy among contacts is 4% in one year from the detection of the index case, then this would mean that among 1,000 contacts, 40 new cases would be detected during this period. However, if all 1,000 contacts receive the chemoprophylaxis and its effectiveness is 50%, 20 cases will be prevented. The NNT would be 50 (1,000/20). In another scenario in which the risk is lower (0.4%) there would be only four cases in one year and the NNT would be 500 (1,000/2). But if NNT is measured for two years and eight cases are detected instead of four, and four cases prevented instead of two, the NNT now would be 250 (1,000/4). This implies that NNT is difficult to be generalized. Table 2 shows the estimates in different studies and these estimates varied from 14 to 265.

How can these estimates be compared with incidence and NNT in contacts in Brazil? In a cohort study done in Rio de Janeiro[20], an incidence rate of 16.94/1,000 person-years was reported. As the mean duration of follow-up was four years, the risk of leprosy among contacts can be estimated as 1-exponential$^{(-\text{ incidence rate x time})6}$ which would give us the value of 6.6%. If PEP protection is assumed to be 50%, the risk of leprosy among contacts submitted to the intervention will be half 6.6%, i.e. 3.3%, and thus the NNT will be 1/(0.066-0.033), which is similar to administering PEP to 30 contacts to prevent one new additional case over four years.

Table 2
Estimate of the number of contacts to receive chemoprophylaxis needed to prevent one case of leprosy (NNT) among contacts

Study: Author, year of first publication, references	Estimate of baseline risk (%) in contacts controls	Estimate of risk in intervention group	Years of follow-up	Estimate of NNT[2]
Moet, 2008[24]	1-2 years: 67 cases in 10,006 = 0.66%	1-2 years 29 in 9951 = 0.29%	2	265[3]
Neelan, 1983[25]	42 cases in 351 = 12.0%	22/358 = 6.1%	3 ½	17
Noordeen, 1976[29]	"non-lepromatous" 109/1000 = 10.9%	72/1000 = 7.2%	3½	27
	"lepromatous" 38/319 = 11.9%	53/636 = 8.3%	5	27
Dharmendra, 1967[10]	2nd survey[1] 41/316 = 13%	19/316 = 6%	3 ½	14
Neelan, 1986[26]	30/280 = 10.7 %	13/280 = 4.6%	~ 4.2	16
Wardekar, 1967[49]	119/11697 = 1.01%	43/11676 = 0.37%	2	154

Note [1]: There is a report with results for the 3rd survey with 5 ½ years[28], but because the amount of missing data, it was chosen to use data from the 2nd survey; [2] the NNT was calculated as 1 ÷ (incidence proportion in control - incidence proportion in intervention); [3] as in the reference.

Whether or not the risk of leprosy among contacts estimated in this study can be generalized to the whole Brazilian scenario is doubtful. For example, 900 cases were reported in 2012 in Sao Luis do Maranhao (population of 1,331,180), which reflects a new case detection rate close to 7/10,000 in the general population[4]. If it were assumed that the risk in contacts is ten times higher than in the general population (a rather high estimate in comparison to the literature), the risk in contacts would be 0.007 and NNT (assuming that protection is 50%) would be 1/(0.007-0.0035) or ~ 285. Most endemic areas have an incidence of leprosy lower than that of Sao Luis do Maranhao. Therefore, it seems that is not easy to generalize results from the studies in different settings.

The role of the PSF

Most municipalities in Brazil are now covered by the Family Health Program (*Programa de Saúde da Familia*, PSF)[34]. Each PSF unit has a team of community health workers (*Agente Comunitário de Saúde*, ACS), and each ACS has a list of all families and individuals in the catchment area. Some potential advantages of integrating the leprosy control activities in the routine of PSF and ACS are presented below.

1. It can facilitate (1) the examination of neighbours without disclosing the diagnosis of the index case, and (2) the adoption of a broader definition of contacts;

2. It would be easier to monitor PEP performance, i.e. the degree to which an intervention operates according to specific standards or guidelines, or achieves results in accordance with stated goals or plans[15], by establishing indicators such as the number of contacts needed to be examined to find one new case among each of the catchment areas, or among households or neighbours of index cases;

3. It would be easier to measure the population impact in the mid -or long- term, as well as monitoring the adverse events due to BCG vaccination and use of chemoprophylaxis;

4. It would be easier to collect data about costs of contact tracing and to estimate the cost to detect one case based on routine, the cost of a more active surveillance and of contact tracing among neighbours, and its sustainability;

5. It would be easier to understand the health care seeking behavior of patients and to implement approaches to manage stigma and to diminish the observed barriers for contact tracing and to seek health services to examination;

6. It would facilitate the implementation of health education programs promoting self-examination;

7. It would facilitate surveillance of cases and contacts, and the routine data can be used to create a cohort of individuals in whom the reduction of disease in contacts and population can be estimated.

However, it is still necessary to acquire a better knowledge on whether the implementation of such intense activities would have negative effects on the other PSF routine activities .

Concluding remarks

What is the next step? Do we need more studies to implement PEP? In our opinion, there is enough evidence supporting the effectiveness of PEP, and the PSF areas seem to be the priority settings where PEP could be implemented. However, other aspects should be considered to make a decision. Firstly, aspects related to sustainability of this intervention should be considered such as cost/effectiveness comparing the different alternatives of intervention, performance monitoring and intervention impact[48]. Secondly, what would be the additional reduction of leprosy occurrence given that (1) the incidence of leprosy is steadily decreasing in Brazil, (2) PEP does not change the social determinants of the disease, and (3) there is evidence that the presence of other public interventions can have an impact in the reduction of leprosy[27].

As PEP benefits and feasibility are not fully established, we recommend that, if a decision is made to start PEP, this should start on a small scale and, as new evidence can be generated, it could provide the basis to move up a scale, or not, to a wider intervention. Some priority municipalities could be chosen to be the first wave of PEP implementation. The National Leprosy Program, alongside the academic community, could also use the opportunity of PEP implementation to plan for some pragmatic epidemiological studies, mimicking routine conditions, that would aim to respond some of the various remaining questions about PEP, such as whether or not to use a broader definition of contacts, the need to use a test to identify contacts with a higher risk, and PEP effects on drug resistance.

RESUMO

Quimioprofilaxia para prevenção de hanseníase e sua implantação no Brasil: uma explicação introdutória para não epidemiologistas

A ocorrência de hanseníase tem diminuído no mundo apesar de que a perspectiva de sua eliminação tem sido questionada. Uma proposta para o controle da endemia é a quimioprofilaxia pós-exposição entre contatos (*post-exposure chemoprophylaxis,* PEP), embora ainda existam dúvidas quanto aos seus aspectos operacionais e generalização de resultados. Nesse texto nós discutimos as evidências disponíveis na literatura, explicamos alguns conceitos epidemiológicos comumente encontrados em pesquisa sobre PEP e a implantação da PEP no contexto brasileiro. Nós argumentamos que: (1) a estimativa em diferentes estudos do numero de contatos necessário para receber PEP para prevenir um novo caso de hanseníase (*number needed to treat*, NNT) não é facilmente generalizável; (2) áreas cobertas pelo programa de saúde da família são as áreas prioritárias onde PEP poderia ser implantado; (3) não existe necessidade de segunda dose da quimioprofilaxia; (4) o risco de resistência à droga usada na PEP parece ser muito pequeno; (5) questionamos a necessidade de teste sorológico para identificar indivíduos entre os contatos que tenham maior risco de doença. Nós opinamos que, se houver uma decisão para se iniciar PEP no Brasil, essa intervenção deveria ser iniciada em pequena escala e, à proporção que novas evidências são geradas sobre a factibilidade, sustentabilidade e impacto da intervenção, a intervenção com PEP poderia ou não ser usada em larga escala.

CONTRIBUTIONS

All of the authors have participated in drafting the manuscript and in reviewing it providing relevant contributions. They have all given the final approval and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTERESTS

None

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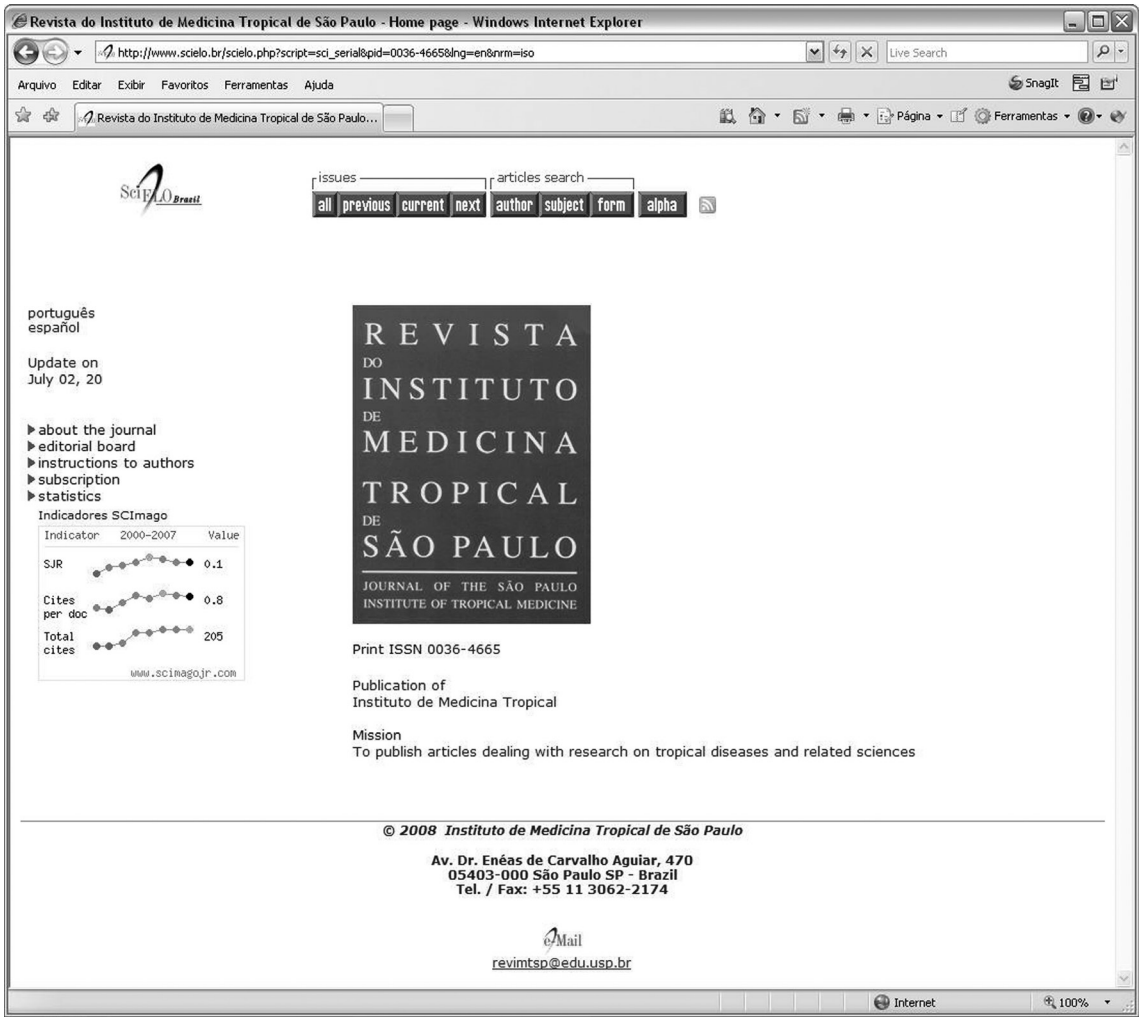

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