Anti-PGL-1 positivity as a risk marker for the development of leprosy: Systematic review and meta-analysis*

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Introduction

Leprosy is an infectious disease caused by Mycobacterium leprae that affects the skin and nerves and can cause significant disability in affected individuals.

In 1991, ten years after the introduction of multidrug therapy (MDT), the World Health Organization (WHO) proposed in the 44th. World Health Assembly, the elimination of leprosy as a public health problem to be reached in 2000. The establishment of such goal reflected optimism similar to that observed after the discovery of dapsone in the 40s of the 20th century. The strategy of eliminating leprosy was based on the assumption that the cure of known leprosy cases would greatly reduce the transmission of Mycobacterium leprae and reduce the burden on health systems by enabling the discharge of those affected. Leprosy is considered eliminated when the prevalence of known cases is less than 1 per 10 000 inhabitants.

In early 2005, the goal of elimination of leprosy was achieved in most of the world, with the exception of nine countries including Brazil (WHO, 2010).

In view of the fact that known prevalence is a function of the detection rate and duration of the event from diagnosis to cure, there are three factors which determinate a limit for the possibility of reducing the known prevalence: the duration of treatment, its effectiveness and the detection rate. Of these three values, only the effectiveness of treatment can be modified up to 100%. It seems clear that the hidden prevalence is responsible for most transmission of leprosy in the scenario where there is effective treatment for the disease and effective government action to ensure universal access to treatment of diagnosed cases. Thus, the reduction in leprosy transmission requires reducing the hidden prevalence by agile detection, to reduce the duration of illness prior to diagnosis / treatment.

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In this perspective, the point prevalence is a known indicator of the burden of disease in a given moment of time, and its change primarily reflects operational changes and not epidemiological (Penna et al, 2008).

Although the prevalence of known cases in the world has been greatly reduced through control programs, the new cases detection rate remains high in some parts of the world, including Brazil.

The detection rate is a function of the actual incidence of cases and of diagnosis agility. If the detection rate is lower than the actual incidence the consequence is the increase in hidden prevalence that is largely responsible for transmitting the disease. Thus, the reduction in leprosy transmission requires reducing the hidden prevalence by agile detection, to reduce the duration of illness prior to diagnosis / treatment. Given that leprosy is not a disease that leads to death, in a situation of lack of access to diagnosis, hidden prevalence can be many times greater than the incidence.

Although there have been years since the introduction of multidrug therapy (MDT), there is no evidence of its impact on the transmission of leprosy. Actually, a better understanding of the transmission of Mycobacterium leprae still is necessary to support control actions with great impact on transmission (Britton & Lockwood, 2004).

The detection rate of new cases of leprosy in Brazil showed upward trend in the last two decades of the twentieth century following the improvement of access to primary health care provided by the development of SUS (Penna et al., 2008), starting downward trend in this first decade of this century (Penna et al, 2009b). The spatial distribution of leprosy shows great heterogeneity, with aggregates (clusters) municipal at high risk (Penna et al., 2009a) presenting as a disease concentrated in the population and the territory.

Currently, the World Health Organization proposes the control of leprosy as a permanent action in areas where transmission persists, with the inclusion of a new target for countries to reduce by 35% between 2011 and 2015 the detection rate of cases with disability degree 2 (WHO, 2012).

In 2010, Brazil had a detection rate of 18.22 cases per 100 000 population and prevalence of 1.56 per 10 000 inhabitants (Ignoti & Paula, 2011).

Undoubtedly the epidemiological dynamics of leprosy is determined by the socioeconomic conditions of the population, and public policies involving socio-economic development, education and reduction of poverty and inequality impact positively in the incidence of this disease. However, a rapid reduction in detection rates of new cases of leprosy was never
Documented. The documented reduction of this rate is slow, being on average 7.3% per year in Norway from 1851 to 1920, resulting in the disappearance of the disease in this country (Irgens, 1980). The highest rate documented annual decline was 14.5% on a year in the Chinese province (Shandong) 1958-1979 (Irgens, 1985).

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A new action to be included in control programs is the use of chemotherapy in people at high risk for developing the disease (WHO, 2012), which probably would bring a greater impact on the transmission of the bacillus than chemotherapy of diagnosed patients. Household contacts of multibacillary patients are at higher risk of developing the disease. A test to identify infection by M. leprae among healthy contacts, screening those with greater risk of developing leprosy, would allow including the chemotherapy of contacts as a control action.

The impossibility of Mycobacterium leprae growing in artificial culture media is a major obstacle to the development of tests to detect infection and disease, forcing the use of animal models. (Duthie et al., 2011).

Serological tests have been developed for the detection of infection and proliferation of Mycobacterium leprae being the most widely used and studied the anti PGL1, IgM (Geluk, 2011).

Spencer and Brenner (2011) present a review article with the history of the development of the test anti PGL1 since the purification of antigen in 1980. These authors suggest that it is an antigen specific to M leprae and suggests that titration of anti PGL1 between contacts can define groups at high risk for developing the disease. However, Sinha et al (2010) showed positivity for anti PGL1 leishmaniasis patients, which would undermine the accuracy of the test in areas where Leishmania infection is frequent.

Systematic review without meta-analysis, published in 2008 concludes that the serologic testing is useful for the classification of patients, monitoring treatment and predicting reactions. This study does not conclude about the value of testing for early diagnosis or as a predictor of illness, stating that "studies indicate that the use of the test can positively influence leprosy control programs" (Moura et al., 2008).

**Rationale**

In this project we intend to conduct a systematic review and meta-analysis of the serological anti PGL-1, aiming to answer the broad question whether the test is able to select individuals
at high risk of developing leprosy. This task is justified not only by the results and controversial views in the literature, but also because in discussions during the XVIII International Congress for Tropical Medicine and Malaria many researchers demonstrated a strong believe that a positive anti PGL-1 IgM have a 100% prediction value for recent infection by M. leprae.

Judgments about the quality of the available evidence and the incorporation of technology into routine health services are complex. The strength of a recommendation or guideline should take into account not only the quality of the evidence, but also the risks of an intervention, such as side effects of chemoprophylaxis and the frequency of its application unnecessary, cost-effectiveness and feasibility of implementing actions a particular health system.

Moreover, the quality of a body of evidence not only relates to types of study involved and methodological quality that ensures the absence of bias or confounding. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (http://www.gradeworkinggroup.org/index.htm) published a series of 12 articles (the 13th. Publication is) in the Journal of Clinical Epidemiology from the the December 2010 with recommendations for the broader assessment of quality of evidence and strength of recommendations.

Thus, besides the systematic review and meta-analysis to be performed, we intend to evaluate the quality of the body of evidence according to the recommendations developed by the GRADE working group.

Currently, as a result of proteome and genome projects are an easier to develop test for antibodies or antigens of pathogens. In the case of neglected diseases, the evaluation of the incorporation of these tests into routine health systems is unlikely to be carried out by research groups in developed countries, leaving Brazil therefore a particularly important role. This type of study also reveals where there are lacks of evidence, helping to define research priorities.

**General Purpose**

Evaluate the applicability of serology PGL-1 for selecting contacts of leprosy patients to chemotherapy

**Specific Objectives**

1. Perform a systematic review of the literature
2. Perform meta-analysis of published data on selected articles
3. Assess the body of evidence as to its quality

4. Evaluate the possibility of incorporating serologic of contacts in leprosy control program.

Methodology

Firstly it is necessary to narrow our question if the test is able to select individuals at high risk of developing leprosy to: “What are the absolute and relative risks of an anti PGL-1 positive patient’s household contact to develop leprosy?”

To answer this question, the review will include only cohort studies, prospective or retrospective, using as control intra-household contacts PGL-1 negative.

All the work of selecting articles and data collection will be conducted by the two researchers then discussed the differences. In the absence of consensus, an outside expert to study will be consulted.

The initial bases to search articles will be PUBMED, which includes MEDLINE, LILACS and the IndMed, database Indian oWPRIM, database western Pacific which includes areas of high incidence of leprosy and the database on international health organization CABI. We will also include research in dissertations and theses, not only from LILACS, as well as the thesis database in England, Germany and seek other theses and dissertations on Google scholar.

Two authors will read all abstracts obtained and selected articles that meet our criteria described above. These articles will be read in full, then suffer new selection in order to be included in the systematic review. A third author will decide about the cases without agreement. Seek new articles in the bibliographies, contact with experts and conference abstracts. In the production of the document with the results of the meta-analysis will follow the recommendations of the declaration SIGMA (Urrutia & Bonfil, 2010).

Each article included will be assessed for its quality. Publication bias will be assessed through funnel chart. Besides observing the differences in method and population sampled in the selected studies, their homogeneity will be evaluated statistically by Chi square, considering \( P<0.10 \) as a sign of heterogeneity, and \( I^2 \) statistics, considering the proportion of variance exceeding the value expected by chance bigger than or equal to 50% as heterogeneity. In these cases, studies will be grouped according to homogeneity. The summary measure may be estimated by using a weighted average using as weight the inverse of the variance of each study. If the dispersion of each study result indicates, we will use the random effect models. We will use sensitivity analysis to evaluate the impact of the inclusion of low-quality articles in the summary measure.
Key words for search will be (contact OR contacts) AND (leprosy OR hansen disease) AND (anti-phenolic glycolipid OR phenolic glycolipid OR anti-PGL-1 OR PGL-1 OR serology).

In PubMed this search is detailed as:


In Lilacs search

(leprosy or Hansen or hanseníase) and (contacto or contato or contactos or contato) and (anti- glicolipídio phenolico OR glicolipídio phenolico OR anti-PGL-1 OR PGL-1 OR sorologia or antiglicolípido fenólico or glicolípido)

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