Risk factors associated with illness in leprosy contacts: a systematic review protocol

Factores de riesgo asociados con la enfermedad en contactos con lepra: un protocolo de revisión sistemática
Fatores de risco associados ao adoecimento em contatos de hanseníase: um protocolo de revisão sistemática

ABSTRACT
Objective: This review will aim to assess the risk factors associated with illness in leprosy contacts. Method: Case-control, cross-sectional and cohort studies, prospective and retrospective studies, experimental studies, from January 2004 to December 2020. Participants will be leprosy contacts. The electronic databases will include VHL, PubMed, Cochrane Library, Embase. Search strategies will be used employing descriptors for each database. The articles will be selected after reading the title and abstract by two independent reviewers. After reading in full, the articles will be selected according to the inclusion criteria. Result: Data will be extracted and tabulated for narrative synthesis. Conclusion: Monitoring contacts is one of the most effective strategies for leprosy control. The identification of risk factors for illness in contacts can contribute to the development of actions in public health. Systematic review registration number: PROSPERO CRD4 2020160680

RESUMEN
Objetivo: Esta revisión tendrá como objetivo evaluar los factores de riesgo asociados con la enfermedad en los contactos con lepra. Método: Estudios de casos y controles, transversales y de cohortes, estudios prospectivos y retrospectivos, estudios experimentales, de enero de 2004 a diciembre de 2020. Los participantes serán contactos leprosos. Las bases de datos electrónicas incluirán BVS, PubMed, Cochrane Library, Embase. Se utilizarán estrategias de búsqueda empleando descriptores para cada base de datos. Los artículos serán seleccionados después de leer el título y el resumen por dos revisores independientes. Después de la lectura completa, los artículos se seleccionarán de acuerdo con los criterios de inclusión. Resultado: los datos se extraerán y tabularán para la síntesis narrativa. Conclusión: El seguimiento de los contactos es una de las estrategias más eficaces para el control de la lepra. La identificación de factores de riesgo de enfermedad en los contactos puede contribuir al desarrollo de acciones en salud pública. Número de registro de revisión sistemática: PROSPERO CRD4 2020160680

RESUMO

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INTRODUCTION

Leprosy is an infectious disease caused by Mycobacterium leprae, also called Hansen’s bacillus, which affects the skin and peripheral nerves. The main route of transmission is through the upper airways. This disease is important for public health, mainly due to its high potential to cause physical disabilities. The host’s immune response to the infection will determine the type of clinical manifestation, depending on the type of lymphocyte activation that leads to a characteristic immunological, clinical and histological spectrum. M. leprae has a multiplication time of 11 to 60 days, considered slow, which justifies the prolonged incubation time and the chronicity of the disease. This microorganism is surrounded by a thick lipid wall 20 nm thick, composed of polyethylene glycol-1 (PGL-1), which is specific for this pathogen. M. leprae has a multiplication time of 11 to 60 days, considered slow, which justifies the prolonged incubation time and the chronicity of the disease. This microorganism is surrounded by a thick lipid wall 20 nm thick, composed of polyethylene glycol-1 (PGL-1), which is specific for this pathogen.

In 2019, 202,185 cases of leprosy were reported worldwide. India and Brazil are the countries with the highest number of cases. Late diagnosis of leprosy is a concern in Brazil, since 10,813 new cases of leprosy were identified in 2019 already in grade 2 disability. The degree of disability is defined by evaluating the patient’s eyes, hands and feet with an interval of 0-2. In grade 0, patients do not show changes; in grade 1, patients had decreased or lost sensitivity; in grade 2, patients have eye changes, such as lagophthalmos and/or ectropion, trichiasis. In the hands and feet, it can present trophic and/or traumatic lesions; claws, resorption, foot drop and ankle contracture. The draft Global Leprosy Strategy for the period 2021-2030 aims to eliminate leprosy by 2030 worldwide. One of the strategies for early diagnosis and treatment is the tracing of leprosy contacts.

Contacts can be defined as people who interact with a diagnosed patient in the home, neighborhood, family or social circle. Previous studies have identified risk factors for illness from contacts with leprosy. Social, nutritional, immunological, genetic risk factors, as well as factors related to the index case, were also described. The following family and social factors were described: consanguinity with the index case, proximity to the index case, social vulnerability, sex and age. Among the immunological factors, positive ML Flow, absence of BCG scar, and negative Mitsuda test in contacts, and close genetic relationship. Factors related to the index case were: being multibacillary, having a high bacilloscopic index and grade 2 disability classification.

The contact exam is indicated for the clinical and epidemiological management of the disease. Assessing scientific evidence helps to improve knowledge about disease risk in the contact group. A preliminary survey of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews was conducted and found no current or ongoing systematic review on the subject. The last review using this approach was published in 2004. This systematic review protocol will aim to assess the risk factors associated with the development of the disease in contacts with leprosy and the guiding question will be: What are the risk factors associated with the development of the disease in contacts with leprosy?
METHOD

The systematic review will be conducted according to the PRISMA-P methodology for systematic reviews of evidence of effectiveness. The systematic review protocol was registered in PROSPERO, under code CRD42020160680. This review will consider eligibility studies investigating contacts with leprosy, including household contacts and social contacts; of both sexes, of any age and will consider studies that compare risk factors for leprosy in contacts and protective factors in healthy contacts.

Studies will be selected without language restriction from 2004 to 2020. Experimental studies will be selected, such as randomized and non-randomized controlled clinical trials, prospective and retrospective cohort studies, case-control studies and cross-sectional analytical studies, without language restriction; Duplicate articles, narrative or systematic review and meta-analysis, general population studies, studies of leprosy patients, case reports of other infectious diseases (acute or chronic), case series, interviews, editorial letters and experimental studies involving animals will be deleted. Published and unpublished studies will be evaluated for eligibility.

The search strategy was focused on published studies. An initial search of the MEDLINE database was performed to identify articles on the topic. The text words in the titles and abstracts of relevant articles and the index terms used to describe the articles were used to develop a complete search strategy for the database and platform. The search strategy, including all keywords and terms from index identified, will be adapted for each source of information included (Appendix 1). Reference lists of all studies selected for critical review will be selected for additional studies. Unpublished studies and gray literature will also be searched for relevant studies.

We consider the following databases as sources of information: Virtual Health Library (VHL), PubMed, Cochrane Library, EMBASE (OVID). Sources of unpublished studies and gray literature to be searched include MedNar, OpenGrey, ProQuest Dissertations and Theses and manual search. After the search, all identified citations will be grouped and uploaded to Rayyan Systems Inc, where duplicates will be identified and removed. After a pilot test, titles and abstracts will be selected by two independent reviewers for evaluation against the inclusion criteria for the review (ESA; ALGO). The full text of selected citations will be evaluated in detail against the inclusion criteria by two independent reviewers (ESA; ALGO). Reasons for excluding full-text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements between reviewers at each stage of the study selection process will be resolved through discussion or with a third or fourth investigator if necessary (NSG).

The results of the research and the study selection and inclusion process will be reported in full in the final systematic review and presented in a flowchart in accordance with PRISMA-P. To assess methodological quality, the two independent reviewers will use standardized instruments to develop a critical assessment of case-control, cross-sectional and cohort studies, prospective and retrospective studies to assess risk factors related to contact with leprosy in the development of the disease. Article authors will be contacted to request missing or additional data for clarification at any stage, if necessary. Any disagreements between reviewers will be discussed and resolved. The results of the assessment of the methodological quality of the studies will be reported in a narrative format and added to a table. All studies, regardless of the methodological quality of the results, will be submitted to data extraction and synthesis, when possible. The results of the critical evaluation using the NEWCASTLE - OTTAWA and ROBINS-I tools will be described descriptively in the review. We will discuss how these results can influence the interpretation of the study evidence.

Studies evaluating the following outcomes will be considered: identification of factors associated with the development of the disease in contacts with leprosy. Factors associated with the index case, such as social, nutritional, genetic and immunological factors, will be of interest in the review. Time and effect measures will be extracted, considering the results obtained in the analysis of relative risk, odds ratio, attributable risk and other measures applicable to the study outcomes.

Data will be extracted from studies independently selected by two reviewers (ESA; ALGO) using Rayyan Systems Inc. Data extracted will include details on population, study methods, exposures and outcomes, as follows:

- Study details: author, year of publication, country.
- Study method/characteristics: the study site and research setting; study design and follow-up, population (number of participants, sex and age); risk factors (all variables investigated in the study); protective factors including all variables investigated in the study; comparative groups;
- Results: protective factors (all variables investigated/explored in the study); main results (risk factors with statistical significance); results (protection factors with statistical significance); cases detected among contacts/precedence or prevalence.
- Data analysis methods: statistical estimates expressed by risk ratio, relative risk ratio, odds ratio, p values and confidence intervals (CI).

Any disagreements that arise between reviewers will be resolved through discussion or with a third reviewer (NSG). We will analyze available data and the impact of lack of data will be considered a limitation of the study, where applicable.

RESULT

Data extracted from selected studies will be synthesized in tables, and
the compiled results will be considered for the development of a meta-analysis. Data synthesis and analysis will be designed to address the research question on risk factors associated with the development of the disease in contacts with leprosy. For each primary study, OR and its standard error will be extracted. For studies with dichotomous variables, they will be obtained from abstracts of logistic regression models, chi-square tests, or Fisher’s exact test, or when not directly available, will be calculated from raw data. For studies with continuous variables, OR estimates will be obtained by transforming linear regression results according to the known relationship between normal and logistic distributions. The results of the studies will be pooled and a general estimate of OR will be obtained from random effects models to explain the heterogeneity of the study. All model estimates will be shown with 95% CIs, and Q statistic, I2 statistic, and tau-square statistic will be used to assess heterogeneity between studies. Forest plots for all meta-analyses will be provided.

In the presence of subgroup differences, meta-regression methods will be used to investigate the effects of categorical or continuous covariates. Publication bias will be investigated using the funnel plot and Egger’s regression test. A p value <0.05 will be considered statistically significant. All analyzes will be conducted using Stata or R. If meta-analysis is not possible, results will be presented in a narrative form, including tables and figures to aid in the presentation of data where appropriate. Topics of interest, such as the identification of factors associated with the development of the disease in leprosy contacts, will be identified and discussed. We will carry out a comprehensive assessment of the methodological quality of the studies. Completion of the review is scheduled for July 2021. Search updates will be performed if necessary.

**DISCUSSION**

This study will allow us to assess the risk factors related to the development of the disease in contacts of leprosy patients. Social, family, nutritional, immunological, genetic aspects will be explored, as well as factors related to the index case, which may be associated with risk factors for illness in the population of contacts, and we will identify protective factors for the development of the disease.

Controlling contacts is one of the strategic pillars for effective surveillance, but it is necessary to carry out the control in a systematic and directed way for greater effectiveness of the control actions. Other authors have already stressed that it is important to structure new studies as a way to support the development of other strategies for leprosy control. Monitoring the high-risk population is necessary to achieve effective leprosy control. The systematization of care and the proposition of light technologies for the care of leprosy contacts is essential for the successful control of the disease and early diagnosis, aiding in an effective surveillance system and contact management. It is expected to offer an approach that contributes to improving scientific knowledge on the subject, providing subsidies for structuring means for better management of the leprosy contact group.

The application of evidence-based health allows exploring and delimiting the risk in this population, as the qualified assessment of the available body of evidence can identify possible strategies applicable to the context of surveillance of contacts. Evidence-based health is defined as a conscious, explicit, and judicious use of the best evidence in the literature.

The potential of this study is to fill a gap in scientific knowledge regarding the determinants of illness in the contact group and the impact of the disease in this population. It is necessary to identify risk factors for the development of the disease to guide the establishment of adequate surveillance strategies for leprosy contacts. The results of this systematic review may contribute to the understanding of the epidemiology of leprosy and the proposition of public health interventions. The results of this study are expected to be available in July 2021.

**CONCLUSION**

It is expected that this work will contribute to the identification and analysis of risk factors related to illness in leprosy contacts. Monitoring contacts is one of the most effective strategies for controlling leprosy. The identification of risk factors for illness in contacts can contribute to the development of public health actions and improvement of the care process.

**REFERENCES**

REFERENCES


Appendix I: Search Strategies for VHL (VHL), MEDLINE (PUBMED), CINAHL (EBSCO), Web of Science (ISI), Cochrane Library, and Embase (OVID) databases

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<th>BASES</th>
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