ABSTRACT

People who interact with leprosy patients in their environment, neighborhood, family, or social relationships are at risk to develop the disease. This systematic review investigated the risk and protective factors associated with the development of leprosy in Brazilian contacts. The studies were found in Cochrane Library, PubMed (MEDLINE), Embase, Virtual Health Library, grey literature and hand search until July 2021. The study selection, data extraction and quality assessment were independently performed by two investigators. The quality assessment was performed using the Newcastle-Ottawa Scale (NOS). This review was registered in PROSPERO (CRD42020160680). Seventeen articles fulfilled the inclusion criteria (n=544). The immunological and molecular factors, such as Anti-phenolic Glycolipid Antibodies (Anti-PGL-1) seropositivity, negative Mitsuda test, absence of Bacillus Calmette-Guérin (BCG) scar, positive Polymerase Chain Reaction (PCR) in blood; age and race; conviviality, education, contact time and type of contact, as well as elements related to the index case (bacilloscopic index; genetic conditions, family relationships), and some combined factors were shown to be relevant risk factors associated with the development of the disease in Brazilian leprosy contacts. The protective factors reported were the presence of one or more BCG scars, positive Mitsuda test, and education level. All selected studies were considered of high quality according to NOS. The knowledge of disease-related risk and protective factors provides the scientific basis for decision-making in the management of the disease in leprosy contacts.

KEYWORDS: Leprosy. Risk factors. Protective factors. Public health surveillance. Systematic review.

INTRODUCTION

Leprosy is an infectious disease caused by Mycobacterium leprae, also known as Hansen’s bacillus, which affects the skin and peripheral nerves. The main route for leprosy transmission is through the upper airways. This disease is important for public health, mainly due to its high potential to cause physical disabilities. The late diagnosis of leprosy is a global concern since 7,198 new cases of leprosy have already been diagnosed with grade-2 disabilities (G2Ds). Most of them were contacts of leprosy patients.

In 2020, 127,396 new cases of leprosy were reported worldwide, comprising 19,195 in the Americas. Brazil is the second country with the highest number of new cases and presents a high burden of the disease. In 2020, 17,979 new cases were reported in Brazil, 8.3% with grade 2 disability. In children, 878 new cases were reported, 4% with grade 2 disability.
Leprosy contacts can be defined as people who interact with an individual diagnosed in their environment, neighborhood, family, or social relationships. A household contact carries an increased risk of developing the disease when compared to the general population\cite{4,4}. Multiple factors that can lead to illness in contacts have been described in the literature encompassing aspects related to the index case (IC)\cite{5}, immunological factors\cite{6-11}, nutritional aspects\cite{12,13}, family relationships, and social factors\cite{5,13-17}, among others. Therefore, the purpose of this systematic review was to investigate factors associated with the development of the disease in Brazilian leprosy contacts.

**MATERIALS AND METHODS**

**Study registration**

This systematic review complies with the Cochrane Handbook for Systematic Reviews of Interventions\cite{18} and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines\cite{19}. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the reference code CRD42020160680. The preliminary version of the study protocol was revised to adapt the inclusion criteria and focus on primary studies developed within the Brazilian population.

**Search strategy and eligibility criteria**

The research question was defined by using the PECO formulation guidance, as follows: Population (P): leprosy contacts; exposure (E): risk factors for leprosy contacts becoming ill; comparator (C): leprosy contacts who did not develop the illness after exposure; outcome (O): illness. The outcomes of interest included the factors associated with the development of the disease in Brazilian leprosy contacts.

The following databases were considered to search for articles: MEDLINE (by PubMed), Embase (by OVID), Cochrane Library, LILACS, WHOLIS, HANSENIASE, IBECS, Health Department of the Sao Paulo State, BDENF – Nursing, CUMED, and BINACIS (by Virtual Health Library). The grey literature was screened on MedNar, OpenGrey and ProQuest. A hand search was also performed in the lists of the selected articles. The complete search strategies and their descriptors were presented in Supplementary Table S1.

No language restrictions were applied to the search, although the full-text review was limited to articles published in English, Spanish, and Portuguese. The period of publication was limited to the period from January 2004 to July 2021, considering the previous systematic review\cite{20}. Studies were eligible for inclusion if: they presented the description of household contacts, peridomiciliary and social leprosy contacts; risk and/or protective factors for healthy Brazilian contacts; observational studies. The choice to include observational studies allowed for the synthetization of data from analytical studies comparing groups of leprosy contacts who developed or did not develop the disease and investigating risk/protective factors with data collected in real-world scenarios. Both genders and different age groups were included. The studies were excluded if they were classified as reviews, case reports, interviews, letters to the editor, or experimental studies.

**Selection of studies and data extraction**

The electronic search results from defined databases were uploaded to the Rayyan Qatar Computing Research Institute\cite{21}. The study selection and data extraction were independently performed by two investigators. A third reviewer resolved any existing disagreements. We used a standardized Microsoft Excel sheet for the data extraction including the author(s), publication year, title, journal, study design, setting, number of study participants, comparative groups (leprosy contacts and healthy participants), gender, age, events among contacts, prevalence or incidence of leprosy among contacts, contact classifications (household, neighbors, and social contacts), and risk and protective factors involved in the development of leprosy among contacts. The funding sources of the studies were also described, when available. The data of risk and protective factors were summarized considering the: immunological factors, genetic aspects, social determinants, factors related to the relationship with the contacts and with the index cases, combined factors, factors related to the index case, and factors in people who were less than 15 years old. The factors were expressed as odds ratios (ORs), adjusted odds ratios (aORs), hazard ratios (HRs), relative risk (RR), adjusted relative risk (aRR), confidence intervals (CI), and/or $p$-values.

**Risk of bias and quality assessment**

The relevant study data were screened and assessed for quality using the adapted Newcastle-Ottawa Scale (NOS). This scale is used for the quality assessment of case-control and cohort studies\cite{22}. The NOS stars awarded for each quality item enabled a quick visual evaluation, with the highest-quality studies awarded nine or more stars. Studies scored above six stars are considered of high quality.
RESULTS

The factors associated with the development of the disease in Brazilian leprosy contacts included sociodemographic, genetic, and immunological variables. The main risk factors reported were Anti-phenolic Glycolipid Antibodies (Anti-PGL-1) seropositivity, negative Mitsuda test, absence of Bacillus Calmette-Guérin (BCG) scars, positive Polymerase Chain Reaction (PCR) in blood; age and race; conviviality, contact time, and type of contact; bacilloscopic index and education of leprosy index cases, as well as consanguinity/family relationships. The presence of BCG vaccine scar, anti-PGL-1 seronegativity, and positive Mitsuda test were described as protective factors. The heterogeneity of the reported variables hindered the comparison among studies and the performance of a meta-analysis. A summary of the selection process of articles is detailed in the PRISMA flow diagram (Figure 1). We identified 544 records from electronic databases and selected 17 studies for this systematic review. We provided a list of all potentially relevant studies that were read in full but were excluded during the selection process (Supplementary Table S2).

Risk factors associated with the illness in leprosy contacts

Immunological factors

Positive Anti-PGL-1/positive ELISA

Seven studies investigated the association between the illness among contacts and the presence of positive PGL-1/positive ELISA\(^8,10,23,29,32,33,35\). One study reported a risk of developing leprosy 5.58 times higher when ML Flow was positive in contacts\(^10\). This result was in line with another study showing that positive Anti-PGL-1 in contacts had a 3.2-fold greater chance of becoming ill compared to those with negative Anti-PGL-1 (OR=3.2; 95% CI: 1.6-6.1)\(^29\).

Other findings related to the risk of illness between positive and seronegative Anti-PGL-1 in contacts included estimates of RR=2.7 (95% CI: 1.29-5.87)\(^32\); RR=5.688 (95% CI: 3.241-9.982)\(^8\); and RR=5.97 (95% CI: 1.45-24.5)\(^33\).

Furthermore, seropositive contacts had a 4.04 times greater chance of neural impairment compared to seronegative contacts (OR=4.04; 95% CI: 1.24-13.21)\(^29\).

Positive Anti-PGL-1 in contacts between 4 and 15 years old was reported to be associated with the development of disease, presenting RR=8.5 (95% CI: 4.0-18.0)\(^23\).

Mitsuda test

Two studies identified an association between the illness and a negative Mitsuda test\(^7,10\). An estimated 6.25-fold increased risk of developing the disease was described for contacts with Mitsuda results ≤7 mm\(^10\) (OR =0.16; 95% CI: 0.07-0.36).
## Table 1 - Study characteristics of the included articles.

| Article numbers | Article Study design | NOS | Classification | Prevalence/Incidence for leprosy contacts detected | Funding sources |
|-----------------|---------------------|-----|----------------|---------------------------------|----------------|
| 1               | Durães et al. 27    | cohort | 254 | 20 | **55/254 (21.7%)** | Household, peridomicile, and social contacts. FAPEMIG, CNPq, and the Brazilian Ministry of Health. |
| 2               | Goulart et al. 18   | cohort | 1,396 | 367 families | **28 (2%)** | Household contacts. |
| 3               | Durães et al. 28    | cohort | 1,098 | 107 | **211 (20.3%)** | Household and peridomicile contacts. |
| 4               | Sales et al. 15     | cohort | 6,158 | 1,201 | **452 (7.3%)** | Household and non-household contacts. |
| 5               | Düppre et al. 29    | cohort | 2,135 | 668 | **48 (2.2%)** | Household contacts. |
| 6               | Sarno et al. 7      | cohort | 7,174 | 1,360 | **75 (3.1%)** | Incidence rate of 0.01694 cases per person-year in the first 5 years of follow-up. |
| 7               | Santos et al. 21    | cohort | 826 | 290 | **26/826 (3.1%)** | Household contacts. |
| 8               | Reis et al. 28      | cohort | 2,092 | 20 | **85 (4.1%)** | Household contacts. |
| 9               | Araújo et al. 8     | cohort | 750 | 1/254 | **12 (1.6%)** | Household and social contacts. |
| 10              | Barreto et al. 32   | cohort | 4,925 | 1 (1.6%) | **8 (0.2%)** | Household and social contacts. |

* NOS: classification system according to Niemi et al., 2010.
* Funding sources: FAPEMIG, CNPq, CAPES, FINEP, and the Brazilian Ministry of Health.
Table 1 - Study characteristics of the included articles. (cont.)

| Article numbers | Article | Study design | Leprosy contacts (n) | Index-cases (n) | Comparative group | Prevalence/Incidence for leprosy contacts detected | Classification | NOS score* | Funding sources |
|-----------------|---------|--------------|---------------------|-----------------|------------------|-----------------------------------------------|---------------|------------|----------------|
| 11              | Araújo et al. [33] | cohort | 104 | -- | -- | 7 (6.7%) | Household contacts | 8 | FAPEMIG, CNPQ, CAPES, and the National Fund for Health (Brazilian Ministry of Health). |
| 12              | Santos et al. [31] | case control | 210 | -- | -- | 175 seropositive household contacts and 35 seronegative household contacts | 4%*(7/175) positive bacilloscopy/ 32.2% (19/59) * neural thickening in the clinical evaluation | Intradomicile and extradomicile contacts. | 8 | CNPq and FAPEMIG |
| 13              | TiemiNagao-Dias et al. [23] | cohort | 68 | -- | -- | 8 (11.8%) | Household and peridomicile contacts | 8 | None |
| 14              | Gomes et al. [24] | cohort | 5,061 | -- | -- | 92/5,036 (1.8%) | Household contacts | 8 | CNPq and FAPEMIG |
| 15              | Manta et al. [25] | cohort | 2,437 | -- | -- | 69 (2.8%) | Household contacts | 8 | LRI, FAPERJ, CNPq, CAPES and the National Fund for Health (Brazilian Ministry of Health) |
| 16              | Teixeira et al. [26] | cohort | 42,725 | 17,876 | -- | 829 (1.9%) | Household contacts | 7 | CNPq, Wellcome Trust, CAPES |
| 17              | Rodrigues et al. [24] | case-control | 204 | -- | -- | 40 children <15 years (ex-intradomiciles and 164 <15 years) | The overall incidence rate was 16.94 per 1,000 people/year of follow-up between 1987 and 1991. | Household and peridomicile contacts | 7 | Applied Research in Health Surveillance (Brazilian Ministry of Health) |

NOS = New-Castle Scale; FAPEMIG = Research Support Foundation of Minas Gerais State; CNPq = Brazilian National Council for Scientific and Technological Development; CAPES = Brazilian Coordination for Improvement of Higher Education Personnel; FINEP = Funding Authority for Studies and Projects; FAPERJ = Research Support Foundation of Rio de Janeiro State; FIOCRUZ = Oswaldo Cruz Foundation; NLR = Netherlands Leprosy Relief; NIH = National Institutes of Health; MALTALEP = Order of Malta; NIAID = National Institutes of Allergy and Infectious Diseases; FAPESP = Amazon Foundation for Studies and Research; SESPA = Secretary of State for Health of Para; UFPA = Universidade Federal do Para; FAPEA-HCFMRP-USP = Teaching, Research and Assistance Support Foundation/Hospital das Clinicas of the Faculty of Medicine of Ribeirao Preto, University of Sao Paulo; PROPESP/UFPA = President’s Office for Research and Undergraduate Studies at the Universidade Federal do Para; FADESP = Research Support and Development Foundation; LRI = Leprosy Research Initiative; FAPERJ = Foundation for Research Support of Rio de Janeiro State. *Above six superior stars: high quality studies by the NOS scale.
### Table 2 - Risk factors associated with illness in leprosy contacts.

| Risk factors | Article                                      | Results | Risk/chance estimates | CI (95%)       | P-value | N Total |
|--------------|----------------------------------------------|---------|-----------------------|----------------|---------|---------|
| **Positive ELISA/ML flow** |                               |         |                       |                |         |         |
| Positive ELISA/ML flow | Goulart et al. 10 | ML flow (PGL-1) | OR=5.58 | 2.56–12.15 | -         | 1,396 |
| Positive ELISA/ML flow | Düppre et al. 29 | PGLI (+) | OR=3.2 | 1.6–6.1 | -         | 2,135 |
| Positive ELISA/ML flow | Barreto et al. 32 | Elisa + anti-PGL-I IgM | OR=2.7 | 1.29–5.87 | <0.01 | 254|
| Positive ELISA/ML flow | Araújo et al. 31 | Elisa anti-PGL-I positive | RR=5.688 | 3.2412–9.9824 | - | 2,992 |
| Positive ELISA/ML flow | Araújo et al. 33 | Anti-PGL-I positive | LR+=3.69/RR=5.97 | [1.67–8.16]/[1.45–24.5] | - | 104|
| Positive ELISA/ML flow | Santos et al. 31 | Elisa positive anti-PGL-I IgM | OR=4.04 | 1.24–13.21 | p=0.020 | 210 |
| Positive ELISA/ML flow | Tiemi Nagao-Dias et al. 35 | PGL-1 positive in contacts from 4 to 15 years | RR=8.5 | 4.0–18.0 | <0.05 | 69|
| **Negative Mitsuda Test** | Goulart et al. 10 | The estimated risk of disease occurrence is 6.25 times higher. for contacts with a Mitsuda result ≤7 mm | OR=0.16 | 0.05–0.46 | - | 1,396 |
| Negative Mitsuda Test | Sarno et al. 7 | Mitsuda reaction negative | OR=3.093 | 1.735–5.514 | <0.001 | - |
| Negative Mitsuda Test | Reis et al. 36 | ML0024 qPCR positivity | OR=14.78 | 3.6–60.8 | <0.0001 | 826 |
| Negative Mitsuda Test | Araújo et al. 33 | Positive qPCR in blood samples | RR/LR+=5.54 | 1.30–23.62 | - | 104 |
| Negative Mitsuda Test | Santos et al. 31 | qPCR in peripheral blood positive | OR=2.08 | 1.08–4.02 | p=0.028 | 210 |
| **BCG scar** | Goulart et al. 10 | The absence of BCG scar risk is 3.7 times higher for contacts without scar | OR=0.27 | 0.13–0.59 | - | 1,396 |
| BCG scar | Sarno et al. 7 | Absence of BCG scar | OR=0.380 | 0.215–0.672 | <0.001 | - |
| BCG scar | Düppre et al. 29 | Higher risk among unvaccinated | OR=1.8 | 8.3–4.6 | 0.03 | 2,135 |
| BCG scar | Düppre et al. 29 | BCG scar in contact PGL1+ | aRR=4.1 | 1.8–8.2 | - | 2,135 |
| **Age** | Manta et al. 25 | Greater than 60 | HR=32.4 | 3.6–290.3 | 0.0001 | 2,437 |
| Age | Teixeira et al. 26 | Older than 50 years | aOR=3.11 | 2.03–4.76 | - | 4,509 |
| Age | Rodrigues et al. 34 | Under 15 years old | aOR=3.41 | 1.24–9.39 | 0.018 | 204 |
| **Breed (skin color)** | Santos et al. 31 | Black and brown skin color (prevalent) | aOR=1.32 | 1.02–1.70 | 0.034 | 7,012 |
| Breed (skin color) | Santos et al. 31 | Black and brown skin color (incidents) | aRR=1.66 | 1.14–2.42 | 0.008 | 6,644 |
| **Education** | Santos et al. 31 | Education up to 4 years | aOR=2.18 | 1.42–3.35 | <0.001 | 4,443 |
| Education | Santos et al. 31 | 4 to 10 years of schooling | aOR=1.33 | 0.81–2.18 | - | 4,443 |
| **Contact time** | Santos et al. 31 | Time of living >5 years with the index case | aOR=1.48 | 1.02–2.15 | 0.041 | 4,443 |
| **Contact type** | Durães et al. 28 | Household contact | aOR=2.44 | 1.69–3.4 | <0.0001 | 1,040 |
| Contact type | Sales et al. 15 | Household contact (co-prevalents) | OR=1.33 | 1.02–1.73 | - | 6,158 |
| Contact type | Santos et al. 31 | Household contact | aOR=1.66 | 1.14–2.42 | 0.008 | 6,644 |
| Contact type | Teixeira et al. 26 | Household contact | aOR=1.48 | 1.17–1.88 | - | 42,725 |
| **Consanguinity/Relationship** | Durães et al. 27 | Consanguineous | OR=2.8 | 1.77–7.74 | - | 197 |
| Consanguinity/Relationship | Durães et al. 28 | First degree kinship | OR=2.42 | 1.75–3.35 | <0.0001 | 1,040 |
| Consanguinity/Relationship | Sales et al. 15 | Consanguineous | OR=1.89 | 1.42–2.51 | - | 6,158 |
| Consanguinity/Relationship | Santos et al. 31 | Spouse, fiance and boyfriend/girlfriend (prevalent) | aOR=1.25 | 0.74–2.11 | - | 7,012 |
| Consanguinity/Relationship | Santos et al. 31 | Parents (prevalent) | aOR=1.69 | 0.97–2.96 | - | 7,012 |
| Consanguinity/Relationship | Santos et al. 31 | Brother (prevalent) | aOR=2.75 | 1.65–4.57 | <0.001 | 7,012 |
| Consanguinity/Relationship | Santos et al. 31 | Son (prevalent) | aOR=2.00 | 1.18–3.39 | 0.01 | 7,012 |
### Table 2 - Risk factors associated with illness in leprosy contacts. (cont.)

| Risk factors               | Article               | Results                                                                 | Risk/chance estimates | CI (95%)       | P-value  | N Total |
|----------------------------|-----------------------|-------------------------------------------------------------------------|-----------------------|----------------|----------|---------|
| Consanguinity/Relationship | Santos et al.91       | Other consanguine relatives (prevalent)                                 | aOR=1.70              | 0.98–2.94      | -        | 7,012   |
|                            | Santos et al.91       | Spouse, fiancé and partner (incidents)                                 | RR=7.53               | 2.51–22.57     | <0.001   | 6,831   |
|                            | Santos et al.91       | Uncle, nephew, cousin, grandfather, and grandson                       | aRR=3.71              | 1.24–11.06     | 0.0019   | 6,831   |
|                            | Santos et al.91       | Parents (incidents)                                                    | aRR=10.93             | 3.48–34.27     | <0.001   | 6,831   |
|                            | Santos et al.91       | Brother (incidents)                                                    | aRR=7.03              | 2.41–20.46     | <0.001   | 6,831   |
|                            | Santos et al.91       | Son (incidents)                                                        | aRR=5.34              | 1.74–16.38     | 0.003    | 6,831   |
| Index case education       | Sales et al.15        | Up to 4 years of schooling                                             | OR=2.72               | 1.54–4.79      | -        | 6,158   |
|                            | Sales et al.15        | 4 to 10 years of schooling                                             | OR=2.40               | 1.30–4.42      | -        | 6,158   |
| Bacilloscopic index of the index case | Sales et al.16 | Bacillary index from one to three compared to IC with BI 0 (co-prevalents) | OR=1.79               | 1.19–2.17      | -        | 6,158   |
|                            | Sales et al.16        | Bacillary index greater than 3 compared to IC with BI 0               | OR=4.07               | 2.73–6.09      | -        | 6,158   |
|                            | Sales et al.16        | Bacillary index from one to three compared to IC with BI 0          | OR=4.30               | 2.12–8.71      | -        | 6,158   |
|                            | Sales et al.16        | Bacillary index greater than 3 compared to IC with BI 0      (co-prevalents) | OR=7.31               | 3.63–14.75     | -        | 6,158   |
|                            | Santos et al.91       | BI 0.1 to 3.0 (incidents)                                             | aRR=3.68              | 1.99–6.82      | <0.001   | 7,012   |
|                            | Santos et al.91       | BI >3 (incidents)                                                     | aRR=5.27              | 2.96–9.38      | <0.001   | 7,012   |
|                            | Santos et al.91       | BI 0.1 to 3.0 (prevalent)                                             | aRR=3.68              | 1.99–6.82      | <0.001   | 6,831   |
|                            | Santos et al.91       | BI >3 (prevalent)                                                     | aRR=5.27              | 2.96–9.38      | <0.001   | 6,831   |
| Factors in children under 15 years old | Rodrigues et al.34 | Age: 8 to 14 years compared to individuals aged 1 to 7 years             | aOR=3.41              | 1.24–9.39      | p=0.018  | 204     |
|                            | Rodrigues et al.34    | Area of residence for children under 15 (rural)                        | aOR=2.60              | 1.11–6.09      | 0.027    | 204     |
|                            | Rodrigues et al.34    | Waste disposal (without garbage collection)                            | aOR=7.31              | 191–2798       | 0.004    | 204     |
|                            | Rodrigues et al.34    | Family history of the disease                                          | aOR=8.76              | 3.41–22.50     | 0        | 204     |
|                            | Rodrigues et al.34    | Contact time greater than 5 years                                     | aOR=3.36              | 1.45–7.78      | 0.005    | 204     |
|                            | Teixeira et al.26     | Male                                                                    | aOR=1.70              | 1.20–2.42      | -        | 20,629  |
| Combined risks             | Goulart et al.10      | Ml flow; Mitsuda Test; BCG Scar                                         | OR=24.47              | 9.7–61.5       | -        | 1,396   |
|                            | Goulart et al.10      | BCG (-) and Mitsuda (+)                                               | OR=19.16              | 8.1–45.5       | -        | 1,396   |
|                            | Barreto et al.32      | Absence of BCG scar, Mitsuda <7mm, and + anti-PGL-I                   | RR=8.109              | 5.1167–12.8511 | -        | 2,992   |

CI = confidence interval; PGL1 = phenolic glycolipid I; ELISA = enzyme-linked immunosorbent assay; OR = odds ratio; RR = relative risk; BCG = Bacillus of Calmette Guérin; LR+ = positive likelihood ratio; qPCR = quantitative polymerase chain reaction; aRR = adjusted relative risk; HR = hazard ratio; aOR = adjusted odds ratio; BI = Bacillary index; aNeural impairment.

0.05-0.46) and a 3-fold increased risk in a cohort followed for 25 years (OR=3.093; 95% CI: 1.735-5.514)7.

**BCG vaccine scars**

Three studies identified an association between illness and the absence of BCG scars7,10,29. They pointed out a 3.7 times higher risk for contacts without a scar10, and a 1.8 times higher risk among unvaccinated contacts7.

Four studies identified that the presence of a BCG vaccine scar was considered a protective factor for developing leprosy8,10,24,31. The presence of at least one BCG vaccine scar showed a 2.44 times greater protection against neural impairment in leprosy contacts35.
Genetic factors

Consanguinity

Four studies have identified the association between illness and consanguinity. The probability of getting sick among consanguineous family members was higher than among non-consanguineous individuals, with estimates reported as OR=2.8 (95% CI: 1.77-7.74)\textsuperscript{15} and OR=1.89 (95% CI: 1.42-2.51)\textsuperscript{15}. When the kinship is of the first degree, the chance of developing leprosy was OR=2.42 (95% CI: 1.75; 3.35)\textsuperscript{28}. Regarding incident cases, the reported risk factors were: being father or mother (aRR=10.93; 95% CI: 3.48-34.27); son (aRR=5.34; 95% CI: 1.74-16.38); brother (aRR=7.03; 95% CI: 2.41-20.46), uncle, nephew, cousin, grandfather and grandson (RR=3.71; 95% CI: 1.24-11.06); wife, fiancé and partner (aRR=7.53; 95% CI: 2.51-22.57). There was also an association between kinship and illness for co-prevalent cases\textsuperscript{31}.

Mycobacterium leprae positive PCR

Two studies identified an association between the illness and a positive PCR\textsuperscript{33,36}. The ML0024 qPCR positivity at the time of diagnosis of the index case showed an OR=14.78 for developing leprosy (95% CI: 3.6-60.8; p<0.0001). Another study suggested the combination of this marker with other prognostic markers for contact management\textsuperscript{36}. The qPCR was positive in blood samples of 104 contacts. The probability of disease outcome was estimated, as well as the relative risk, by comparing the results of the household contacts who had the disease with the results of those without clinical manifestations during the follow-up (LR+ and RR=5.54; 95% CI: 1.30-23.62)\textsuperscript{33}. Another study identified that positivity for qPCR in peripheral blood presented a 2.08 times higher concerning the neural impairment in leprosy contacts (OR=2.08; 95% CI: 1.08-4.02)\textsuperscript{35}.

Sociodemographic determinants

Age

Three studies identified the age of the contact as a risk factor associated with illness. Overall, there was a variation for extreme ages, such as children younger than 15 years old (aOR=3.41; 95% CI: 1.24-9.39), contacts older than 50 years old (aOR=3.11; 95% CI: 2.03-4.76)\textsuperscript{26}, and also people older than 60 years old (HR=32.4; 95% CI: 3.6-290.3)\textsuperscript{35}.

Ethnicity

Being of African descent and having black or brown skin color were reported to have a RR=1.66 among incident cases (95% CI: 1.14-2.42) and aOR=1.32 for prevalent cases (95% CI:1.02-1.70)\textsuperscript{31}.

Education

One study identified the association between the schooling of the contact and leprosy disease. In the analysis of prevalent cases, an aOR=1.33 (95% CI: 0.81-2.18) was identified in contacts who had between 4 and 10 years of schooling, and aOR=2.18 (95% CI: 1.42-3.35) for contacts with less than 4 years of schooling\textsuperscript{31}.

Factors related to cohabitation

Four studies identified an association between illness and type of contact. The risk of becoming ill among household contacts was confirmed with aOR=2.44 (95% CI: 1.69; 3.4) when compared to non-household contacts\textsuperscript{28}, OR=1.96 (95% CI: 1.29-2.98) for incident cases\textsuperscript{15}, and OR=1.33 (95% CI: 1.02-1.73) for co-prevalent cases, which was in line with another study\textsuperscript{31} presenting aOR=1.33 (95% CI: 1.00-1.77) for co-prevalent cases. An OR=1.48 (95% CI: 1.17-1.88) was reported for household contacts of the multibacillary patients\textsuperscript{26}. One study identified an association between illness and the time living together and/or cohabiting, showing that the longer the time of exposure to the bacillus, the greater the chance of becoming ill\textsuperscript{31}. Living together for over 5 years with the index case showed an aOR=1.48 (95% CI: 1.02-2.15) for becoming ill when analyzing the prevalent cases\textsuperscript{31}.

Factors related to the index case

Regarding the index case, the relevant factors for the development of the disease in the group of contacts were education and bacilloscopic index. For prevalent cases, the chance of becoming ill among contacts of multibacillary patients with bacillary index (BI) from one to three presented an OR=1.79 (95% CI: 1.19-2.17) when compared to the index case with BI zero. For BI higher than 3, the result was OR=4.07 (95% CI: 2.73-6.09) when compared to patients with BI zero\textsuperscript{15}.

For incident cases, the chance of developing illness for contacts of a leprosy patient with BI higher than 3 was RR=5.27 (95% CI: 2.96-9.38) and for contacts of patients with BI between 0.1 to 3 was aRR=3.68 (95% CI: 1.99-6.82)\textsuperscript{35}. The index case for education up to 4 years showed an OR=2.72 (95% CI: 1.54-4.79) and education from 4 to 10 years presented an OR=2.40 (95% CI: 1.30-4.42), being a risk factor among co-prevental cases\textsuperscript{15}. 
Combined risks

Two studies identified an association between BCG, ML Flow, Mitsuda test, and the development of leprosy among the contacts\textsuperscript{8,10}. The relationship between the amount of BCG scars, Mitsuda test, and ML Flow serological test was identified. The presence of one or two BCG vaccine scars among the leprosy contacts showed a higher cellular immune response in the Mitsuda test.

Factors in children under 15 years old

The following factors were associated with leprosy after adjustments: age (OR=3.41; 95% CI: 1.24-9.39), residence area (OR=2.60; 95% CI: 1.11-6.09), garbage disposal (OR=7.31; 95% CI: 1.91-27.98), family history of the disease (OR=8.76; 95% CI: 3.41-22.50), and length of residence (OR=3.36; 95% CI: 1.45-7.78)\textsuperscript{26}.

Becoming ill among individuals aged from 8 to 14 years old presented an OR=3.4 (95% CI: 1.24-9.39) when compared to individuals aged from 1 to 7 years old. Those living in rural areas who developed the disease presented an OR=2.6 (95% CI: 1.11-6.09) compared to people living in urban areas. Developing leprosy had an OR=7.3 (95% CI: 1.91-27.98) when garbage was burned or buried compared to those with access to garbage collection. Children with a family history of leprosy presented an OR=8.76 (95% CI: 3.41-22.50) to develop the disease compared to those with no family history. The probability of leprosy occurrence was 3.3 times higher when living in a residence for more than 5 years with the index case than living for less time in the same residence\textsuperscript{26}.

Protective factors against illness in leprosy contacts

The protective factors against illness were the presence of one or more BCG vaccine scars\textsuperscript{8,10,24,31,35}, positive Mitsuda test\textsuperscript{8} and the level of education of leprosy contacts\textsuperscript{26}. The protective factors are described in Table 3.

DISCUSSION

This systematic review described the factors associated with the development of disease in leprosy contacts of the Brazilian population. In this review, all selected studies were classified as of high quality which indicates the consistency of their results. Most studies were funded by organizations with no potential economic interests, which may contribute to a more independent interpretation of the data. The identification of risk and protective factors in the Brazilian population can substantiate the establishment of strategies for early case detection, monitoring of leprosy contacts, and controlling the disease, helping health managers to improve the effectiveness of actions in public health. The heterogeneity of the variables described revealed the complexity of assessing a neglected disease and may compromise the identification of important factors to be considered for decision-making in healthcare. A broad overview of risk and protective factors was provided to enrich the discussion on the disease development process in leprosy contacts.

Table 3 - Protective factors against illness in leprosy contacts.

| Protective Factors | Article | Results | Statistical results | CI (95%) | p-value | N Total |
|--------------------|---------|---------|---------------------|----------|---------|---------|
| **BCG scars**      |         |         |         |          |         |         |
| One or more BCG scars | Goulart et al.\textsuperscript{10} | 72.9% – 0.27 | 0.13–0.59 | - | 1,396 |
| Presence of BCG scar | Santos et al.\textsuperscript{31} | OR=0.30 | 0.22–0.41 | - | 7,174 |
| Presence of BCG scar | Santos et al.\textsuperscript{31} | 0.22–0.41 | 0.44–0.90 | - | 7,174 |
| Two or more BCG scars | Araújo et al.\textsuperscript{8} | RR=0.0459 | 0.006–0.338 | - | 2,992 |
| Two scars compared to no BCG scars | Gomes et al.\textsuperscript{24} | RR=0.41 | 0.2016–0.8319 | p= 0.007 | 5,661 |
| One BCG scar | Santos et al.\textsuperscript{31} | OR =0.41 | 0.18–0.98 | p= 0.044 | 210 |
| **Positive Mitsuda Test** | | | | | | |
| Mitsuda reactions >7 mm compared to 0-3 mm reactions | Araújo et al.\textsuperscript{8} | RR= 0.1446 | 0.0566–0.3696 | - | 2,992 |
| **Education/ schooling** | | | | | | |
| No schooling or preschool | Teixeira et al.\textsuperscript{26} | aOR=0.59 | 0.38–0.92 | - | 819 |

OR = odds ratio; RR = relative risk; aOR = adjusted odds ratio.
Immunological factors

The selected studies confirmed the importance of Anti-PGL-1 serology for the identification of contacts at higher risk of illness. It is known that Anti-PGL-1 serology has a strong association with smear microscopy since the gradual increase in BI is accompanied by a semiquantitative increase in antibody levels measured by the test. The findings corroborate other studies, which identified that this test helps to detect contacts that tend to develop leprosy regardless of the clinical form of the index case and that illness among seropositive individuals can vary from 2 to 13%. A systematic review and meta-analysis of cohort studies classified contacts according to positivity for Anti-PGL-1 in the first assessment with at least a one-year follow-up showed that contacts who were Anti-PGL-1 positive at the start of the study were three times more likely to develop leprosy. These data reinforce the importance of testing to monitor leprosy contacts.

The Mitsuda test helps with the diagnosis of leprosy, especially when combined with other tests, and can also be useful for monitoring household and social contacts of leprosy patients. The results found regarding the Mitsuda test have also been elucidated by other authors. The Mitsuda positive reactions were observed between 59% and 88.2% of healthy contacts, and the proportion of positive reactions may increase with age. In a study with leprosy patients, the participation of the allele HLA-DQ1 in the absence of response to the Mitsuda test has been reported. Then, new studies that investigate cellular immunity in leprosy contacts would contribute substantially to getting new biomarkers.

Regarding the BCG vaccine scars, the increased immune response against leprosy after vaccination has already been demonstrated, and the administration of an additional dose of BCG has been reported to be even more protective. A meta-analysis identified a protective effect of BCG of 26% among experimental studies and 61% among observational studies. The protection was greater against multibacillary forms of leprosy compared to paucibacillary forms. Another meta-analysis also confirmed that there is sufficient and convincing evidence for the protective effect of BCG vaccination against leprosy in patients.

The protective effect of BCG vaccination has been demonstrated with a range of 20-90%, and there is consistent evidence for its role in reducing the incidence of leprosy. These findings support the introduction of BCG vaccination as a protective factor against the development of leprosy among contacts, and the absence of vaccine scar as a risk factor to become ill.

In summary, there is an association between Anti-PGL-1, IgM serology, Mitsuda test, and BCG scars with the risk of illness, especially when these factors are combined. Some follow-up studies on the illness of leprosy contacts positively correlated BCG scars, Mitsuda test, and ML Flow result. These results indicate the importance of performing these tests for the surveillance of leprosy contacts.

Genetic conditions

Consanguinity has been reported to be a risk factor for developing illness in leprosy contacts. Genetic-based studies have identified polymorphisms that may be associated with susceptibility to leprosy in index cases and contacts. Genetic and/or environmental factors may exert a crucial influence on the transmission of M. leprae infection and/or the pathogenesis of leprosy. There is a close genetic relationship in leprosy among family members, especially between children, parents, and siblings.

The blood PCR should be considered as a risk factor, but associated with other factors, reinforcing the importance of considering not only genetic factors but also other ones for a better understanding of the disease process. Blood PCR presented in leprosy contacts high sensitivity and allowed the detection of bacterial cells from the amplification of DNA fragments. For detection of the M. leprae bacillus, blood samples, cellular scrapings, skin biopsy, nerve, and nasal secretion can be used. However, in this review, positive PCR in the blood has been reported to be a risk factor for becoming ill and for nerve involvement in leprosy contacts.

Sociodemographic factors

Precarious living conditions have been reported to contribute to the persistence of leprosy transmission. Social inequality increases the susceptibility to various diseases, including leprosy. Another study reported an association between the development of leprosy and social conditions, even though these associations would not necessarily imply a causal connection corroborating the findings of this review. Education level has been reported as a risk and protective factor. Several studies pointed to a higher chance of getting sick with leprosy in the lower economic class population.

An integrative review discussed that leprosy is highly influenced by the social context in which the patient is embedded. It has been emphasized that it is important to consider the socioeconomic factors to identify unfavorable indicators supporting the development of practices to reduce inequalities in the process of care for leprosy patients.
These practices should go beyond health care, bringing an intersectoral articulation, with systemic and social care for leprosy patients.

Regarding proximity with the index case, it was observed that household contacts have a greater chance of becoming ill\textsuperscript{29,57}, but it is necessary to consider that social contacts also need to be monitored to control the disease. Being a spouse or boy/girlfriend would increase the chances of becoming ill\textsuperscript{31}. This fact can be explained by the type of interaction with the index case in which the contacts have intimate and prolonged interaction with the patient. Most factors related to index cases are associated with the transmissibility of the disease. These refer to the number of bacilli to which the contacts would be exposed, increasing the risk of transmission. The low education of the index case has also been reported as a risk factor probably due to poor living conditions\textsuperscript{56}.

In children, the factors associated with the disease showed the greater vulnerability of children aged 8 to 14 years old, associated with living conditions and time of residence, as well as family history of the disease. Illness in children showed that the disease is continuous, that there are undetected patients, and that there is the persistence of leprosy transmission in the community\textsuperscript{58}.

This study described the scientific evidence related to the development of leprosy in Brazilian contacts by synthesizing their various immunological, genetic and sociodemographic factors. The disease-related factors in leprosy contacts have been studied and provide the scientific basis for decision-making in disease management. However, establishing a causal relationship is still a challenge, in addition to the dynamics of convivial relationships and sociodemographic conditions.

**CONCLUSION**

The Anti-PGL-1 seropositivity, negative Mitsuda test, absence of BCG scar, positive PCR in blood; age and race; conviviality, education, contact time and type of contact, as well as elements related to the index case (bacilloscopic index; genetic conditions, family relationships), and some combined factors (e.g., Mitsuda, Anti-PGL-1, BCG scar) were shown to be relevant risk factors associated with the development of disease in Brazilian leprosy contacts. The protective factors reported were the presence of one or more BCG scars, positive Mitsuda test, and education level. The knowledge of disease-related risk and protective factors provides the scientific basis for decision-making in the management of leprosy in contacts and may substantiate the development of strategies for disease monitoring.

**ACKNOWLEDGMENTS**

This study received administrative support from the Graduate Program in Health Sciences: Infectious Diseases and Tropical Medicine. MOCR is a research fellow of the Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq) and holds a productivity scholarship.

**CONFLICT OF INTERESTS**

None of the authors had any financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

**FUNDING**

This study was funded in part by the Coordenacao de Aperfeicoamento de Pessoal de Nivel Superior (CAPES). Financial Code 001.

**REFERENCES**

1. Walker SL, Lockwood DN. Leprosy. Clin Dermatol. 2007;25:165-72.
2. World Health Organization. Global leprosy (Hansen disease) update, 2020: impact of COVID-19 on global leprosy control: weekly epidemiological record. [cited 2022 Aug 11]. Available from: https://www.who.int/publications/i/item/who-wer9636-421-444
3. Bührer-Sékula S, Smits HL, Gussenhoven GC, van Leeuwen J, Amador S, Fujiwara T, et al. Simple and fast lateral flow test for classification of leprosy patients and identification of contacts with high risk of developing leprosy. J Clin Microbiol. 2003;41:1991-5.
4. Douglas JT, Cellona RV, Fajardo TT Jr, Abalos RM, Balagon MV, Klatser PR. Prospective study of serological conversion as a risk factor for development of leprosy among household contacts. Clin Vaccine Immunol. 2004;11:897-900.
5. Carvalho AP, Fabri AC, Oliveira RC, Lana FC. Factors associated with anti-phenolic glycolipid-I seropositivity among the household contacts of leprosy cases. BMC Infect Dis. 2015;15:219.
6. Hacker MA, Duppre NC, Nery JA, Sales AM, Sarno EN. Characteristics of leprosy diagnosed through the surveillance of contacts: a comparison with index cases in Rio de Janeiro, 1987-2010. Mem Inst Oswaldo Cruz. 2012;107 Suppl 1:49-54.
7. Sarno EN, Duppre NC, Sales AM, Hacker MA, Nery JA, Matos HJ. Leprosy exposure, infection and disease: a 25-year surveillance study of leprosy patient contacts. Mem Inst Oswaldo Cruz. 2012;107:1054-9.
8. Araujo S, Rezende MM, Sousa DC, Rosa MR, Santos DC, Goulart
22. Wells GA, Shea B, O’Connell D, Peterson J, Welch V, Losos MT, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. [cited 2022 Aug 11]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm

23. TiemiNagao-Dias A, Macedo AC, Rodrigues RO, Pedroza FH, Albuquerque AA, Moreira FA, et al. Serum anti-PGL-1 IgG, IgM, and IgA in a 3-year follow-up study of 4–15-year-old leprosy contacts. Pediatr Infect Dis J. 2019;38:e193-8.

24. Gomes RR, Antunes DE, Santos DF, Sabino EF, Oliveira DB, Gaulart IM. BCG vaccine and leprosy household contacts: protective effect and probability to becoming sick during follow-up. Vaccine. 2019;37:6510-7.

25. Manta FS, Barbieri RR, Moreira SJ, Santos PT, Nery JA, Duppre NC, et al. Quantitative PCR for leprosy diagnosis and monitoring in household contacts: a follow-up study, 2011–2018. Sci Rep. 2019;9:16675.

26. Teixeira CS, Pescarini JM, Alves FJ, Nery JS, Sanchez MN, Teles C, et al. Incidence of and factors associated with leprosy among household contacts of patients with leprosy in Brazil. JAMA Dermatol. 2020;156:640-8.

27. Düräes SM, Guedes LS, Souza MJ, Cavaliere FA, Oliveira ML. Estudo de 20 focos familiares de hanseníase no município de Duque de Caxias, Rio de Janeiro. An Bras Dermatol. 2005;80 Supl 3:S295-300.

28. Düräes SM, Guedes LS, Souza MD, Magnanini MM, Oliveira ML. Epidemiologic study of 107 cases of families with leprosy in Duque de Caxias, Rio de Janeiro, Brazil. An Bras Dermatol. 2010;85:339-45.

29. Düppre NC, Camacho LA, Sales AM, Ilarremendi X, Nery JA, Sampaio EP, et al. Impact of PGL-1 seropositivity on the protective effect of BCG vaccination among leprosy contacts: a cohort study. PLoS Negl Trop Dis. 2012;6:e1711.

30. Liu PT, Wheelwright M, Teles R, Komisopoulou E, Edfeldt K, Ferguson B, et al. MicroRNA-21 targets the vitamin D–dependent antimicrobial pathway in leprosy. Nat Med. 2012;18:267-73.

31. Santos DS, Duppre NC, Sales AM, Nery JA, Sarno EN, Hacker MA. Kinship and leprosy in the contacts of leprosy patients: cohort at the Souza Araújo Outpatient Clinic, Rio de Janeiro, RJ, 1987–2010. J Trop Med. 2013;2013:596316.

32. Barreto LG, Bisanzio D, Frade MA, Moraes TM, Gobbo AR, Guimarães LS, et al. Spatial epidemiology and serologic cohorts increase the early detection of leprosy. BMC Infect Dis. 2015;15:527.

33. Araujo S, Freitas LO, Gaulart LR, Gaulart IM. Molecular evidence for the aerial route of infection of Mycobacterium leprae and the role of asymptomatic carriers in the persistence of leprosy. Clin Infect Dis. 2016;63:1412-20.

34. Rodrigues TS, Gomes LC, Cortela DC, Silva EA, Silva CA, Ferreira SM. Factors associated with leprosy in children contacts of notified adults in an endemic region of Midwest Brazil. J Pediatr (Rio J). 2020;96:593-9.

35. Santos DF, Mendonça MR, Antunes DE, Sabino EF, Pereira RC, Gaulart LR, et al. Molecular, immunological and neurophysiological evaluations for early diagnosis of neural
Factors associated with the development of leprosy in Brazilian contacts: a systematic review

impairment in seropositive leprosy household contacts. PLoS Negl Trop Dis. 2018;12:e0006494.

36. Reis EM, Araujo S, Lobato J, Neves AF, Costa AV, Gonçalves MA, et al. Mycobacterium leprae DNA in peripheral blood may indicate a bacilli migration route and high-risk for leprosy onset. Clin Microbiol Infect. 2014;20:447-52.

37. Santos GG, Marcucci G, Guimarães Júnior J, Margarido LC, Lopes LH. Pesquisa de Mycobacterium leprae em biópsias de mucosa oral por meio da reação em cadeia da polimerase. An Bras Dermatol. 2007;82:245-9.

38. Santos AR, Degrave WM, Suffys PN. Use of polymerase chain reaction (PCR) in leprosy research. Indian J Lepr. 1999;71:101-10.

39. Bührer-Sékula S. PGL-I leprosy serology. Rev Soc Bras Med Trop. 2008;41 Suppl 2:3-5.

40. Moura RS, Calado KL, Oliveira ML, Bührer-Sékula S. Leprosy serology using PGL-I: a systematic review. Rev Soc Bras Med Trop. 2008;41 Suppl 2:11-8.

41. Brasil MT, Oliveira LR, Rimoli NS, Cavallari S, Gonçalves OS, Lessa JL., et al. Sorologia anti PGL-1 e risco de ocorrência de hanseníase em área de alta endemicidade do Estado de São Paulo: quatro anos de seguimento. Rev Bras Epidemiol. 2003;6:262-71.

42. Penna ML, Penna GO, Iglesias PC, Natal S, Rodrigues LC. Anti-PGL-1 Positivity as a risk marker for the development of leprosy among contacts of leprosy cases: systematic review and meta-analysis. PLoS Negl Trop Dis. 2016;10:e0004703.

43. Lastória JC, Abreu MA. Leprosy: review of the epidemiological, clinical, and etiopathogenic aspects - Part 1. An Bras Dermatol. 2014;89:205-18.

44. Beiguelman B. A reação de Mitsuda depois de oitenta anos. Hansenol Int. 1999;24:144-61.

45. Arruda MS, Arruda OS, Astolfi CS, Opromolla DV. Estudo das reações de Fernandez e Mitsuda em pacientes hansenianos e seus contatos. Hansenol Int. 1985;10:23-31.

46. Convit J, Avila JL, Goihman M, Pinardi ME. A test for the determination of competency in clearing bacilli in leprosy patients. Bull World Health Organ. 1972;46:821-6.

47. Cardona-Castro NM, Restrepo-Jaramillo S, de la Ossa MG, Brennan PJ. Infection by Mycobacterium leprae of household contacts of lepromatous leprosy patients from a post-elimination leprosy region of Colombia. Mem Inst Oswaldo Cruz. 2005;100:703-7.

48. Contin LA, Alves CJ, Fogagnolo L, Nassif PW, Barreto JA, Lauris JR, et al. Use of the ML-Flow test as a tool in classifying and treating leprosy. An Bras Dermatol. 2011;86:91-5.

49. Souza FC, Marcos EV, Ura S, Opromolla PA, Nogueira ME. Estudo comparativo entre reação de Mitsuda e antígenos leucocitários humanos em pacientes hansenianos. Rev Soc Bras Med Trop. 2007;40:188-91.

50. Zodpey SP, Ambadekar NN, Thakur A. Effectiveness of Bacillus Calmette Guerin (BCG) vaccination in the prevention of leprosy: a population-based case-control study in Yavatmal District, India. Public Health. 2005;119:209-16.

51. Moet FJ, Oskam L, Faber R, Pahan D, Richards JH. A study on transmission and a trial of chemoprophylaxis in contacts of leprosy patients: design, methodology and recruitment findings of COLEP. Lepr Rev. 2004;75:376-88.

52. Moraes MO, Cardoso CC, Vanderboort PR, Pacheco AG. Genetics of host response in leprosy. Lepr Rev. 2006;77:189-202.

53. Manry J, Nédélec Y, Fava VM, Cobat A, Orlova M, Van Thuc N, et al. Deciphering the genetic control of gene expression following Mycobacterium leprae antigen stimulation. PLoS Genet. 2017;13:e1006952.

54. Oliveira AL, Chaves AT, Menezes CA, Guimarães NS, Bueno LL, Fujiwara RT, et al. Vitamin D receptor expression and hepcidin levels in the protection or severity of leprosy: a systematic review. Microbes Infect. 2017;19:311-22.

55. Goltzman D, Hendy GN, White JH. Vitamin D and its receptor during late development. Biochim Biophys Acta. 2015;1849:171-80.

56. Leano HA, Araújo KM, Bueno IC, Niitsuma EN, Lana FC. Socioeconomic factors related to leprosy: an integrative literature review. Rev Bras Enferm. 2019;72:1405-15.

57. Khadge S, Banu S, Boboška K, Schip JJ, Goulart IM, Thapa P, et al. Longitudinal immune profiles in type 1 leprosy reactions in Bangladesh, Brazil, Ethiopia and Nepal. BMC Infect Dis. 2015;15:477.

58. Pires CA, Malcher CM, Abreu Júnior JM, Albuquerque TG, Corrêa IR, Daxbacher EL. Leprosy in children under 15 years: the importance of early diagnosis. Rev Paul Pediatr. 2012;30:292-5.

Supplementary Material available from: https://doi.org/10.48331/scielodata.34HR6l