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REVIEW

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Factors associated with the development of leprosy in Brazilian contacts: a systematic review

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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[1]. 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[2].

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[2].

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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[3,4]. Multiple factors that can lead to illness in contacts have been described in the literature encompassing aspects related to the index case (IC)[5], immunological factors[4,6-11], nutritional aspects[12,13], family relationships, and social factors[8,13-17], 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[18] and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines[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[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[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[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).

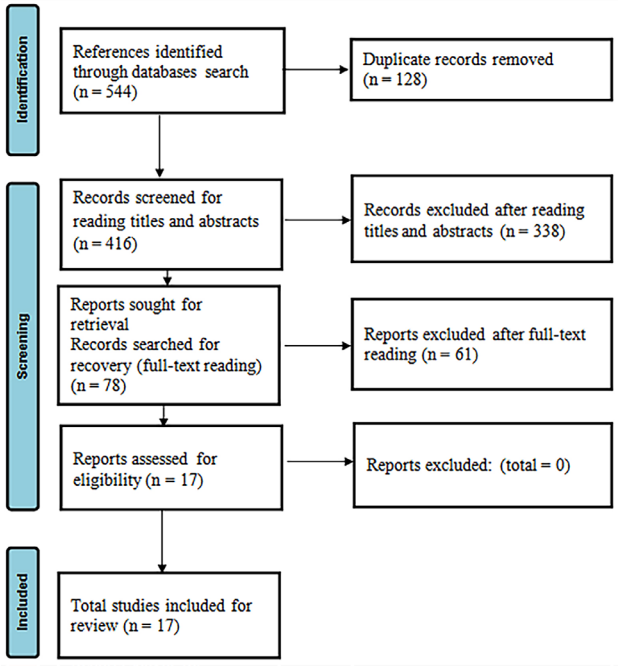

Figure 1 – PRISMA 2020 flow diagram summarizing the systematic search and review process.

Study characteristics

The summary of the studies is shown in Table 1 and Table 2. Of the 17 reports, 72,876 leprosy contacts were enrolled. Regarding the study design, 15 cohort[7,8,10,15,23-33] and two case-control studies[34,35] were included in this review. All selected studies were considered of high quality according to NOS with scores of 7 and 8 (Table 1). The details on the assessment of the quality of studies using the NOS are presented in Supplementary Table S3. Most studies (13; 76.5%) were funded, comprising eleven studies funded by the Brazilian government or its partnership with Brazilian research agencies[10,15,24-26,29,31-34,36], and three were funded by an international non-governmental organization (Netherlands Leprosy Relief)[27-29].

Most studies recruited contacts in outpatient settings (70.6%), followed by home visits (23.5%) and population-based studies with medical record reviews (5.9%). Most studies were conducted in the Southeastern region (64.7%), followed by the Northeastern (11.7%), Northern (5.8%), and Central-western (5.8%) regions, as well as national-level studies (12%). The age of the participants ranged from 0 to 90 years old. Twelve studies addressed only household contacts and five addressed household, social, and neighborhood contacts.

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: 3.2412-9.9824)[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)[35]. 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:

Table 1 - Study characteristics of the included articles.

Article numbers	Article	Study design	Leprosy contacts (n)	Index-cases (n)	Comparative group	Prevalence/Incidence for leprosy contacts detected	Classification	NOS score*	Funding sources
1	Durães *et al.*[27]	cohort	254	20	--	55/254 (21.7%)	Household, peridomicile, and social contacts	7	NLR
2	Goulart *et al.*[10]	cohort	1,396	367 families	--	28 (2%)	Household contacts	8	FAPEMIG, CNPq, CAPES, FINEP, and the Brazilian Ministry of Health
3	Durães *et al.*[28]	cohort	1,098	107	--	211 (20.3%)	Household and, peridomicile contacts	7	NLR
4	Sales *et al.*[15]	cohort	6,158	1,201		452 (7.3%)	Household and non-household contacts	8	CNPq, FAPERJ, and FIOCRUZ
5	Düppre *et al.*[29]	cohort	2,135	668	--	46 (2.2%) coprevalent/ (60) 2.8% incidence. Incidence density of 5.08 per 1,000 people/year	Household contacts	8	FIOCRUZ, the Brazilian Ministry of Health, NLR and CNPq
6	Sarno *et al.*[7]	cohort	--	--	--	Incidence rate of 0.01694 cases per person-year in the first 5 years of follow-up	Household contacts	8	None
7	Santos *et al.*[31]	cohort	7,174	1,360	--	incidence of 2.01 per 1,000 people/year.	Household, family, and social contacts.	8	None
8	Reis *et al.*[36]	cohort	826	200	--	26/826 (3.1%)	Household contacts	8	FAPEMIG, CNPq, CAPES and the National Fund for Health (Brazilian Ministry of Health).
9	Araújo *et al.*[8]	cohort	2,992	--	--	75 (2.5%)	Household contacts	8	None
10	Barreto *et al.*[32]	cohort	750 time 1/ 254 time 2	--	--	43/254 (16.9%)	Household and social contacts	8	CNPq, CAPES, CAPES PROAMAZONIA, FAPESPA, SESPA, UFPA, FAEPA-HCFMRP-USP, NIH, MALTALEP, NIAID, PROPESP/UFPA and FADESP

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.*[34]	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; FAPESPA = Amazon Foundation for Studies and Research; SESPA = Secretary of State for Health of Para; UFPA = Universidade Federal do Para; FAEPA-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	Goulart *et al.*[10]	ML flow (PGL-1)	OR=5.58	2.56–12.15	-	1,396
	Düppre *et al.*[29]	PGLI (+)	OR=3.2	1.6–6.1	-	2,135
	Barreto *et al.*[32]	Elisa + anti-PGL-I IgM	OR=2.7	1.29–5.87	<0.01	254
	Araújo *et al.*[8]	Elisa anti-PGL-I positive	RR=5.688	3.2412–9.9824	-	2,992
	Araújo *et al.*[33]	Anti-PGL-I positive	LR+=3.69/ RR=5.97	[1.67–8.16]/ [1.45–24.5]	-	104
	Santos *et al.*[31]	Elisa positive anti-PGL-I IgM[a]	OR=4.04	1.24–13.21	p=0.020	210
	TiemiNagao-Dias *et al.*[23]	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
	Sarno *et al.*[7]	Mitsuda reaction negative	OR=3.093	1.735–5.514	<0.001	-
Positive PCR in blood	Reis *et al.*[36]	ML0024 qPCR positivity	OR=14.78	3.6–60.8	<0.0001	826
	Araújo *et al.*[33]	Positive qPCR in blood samples	RR/LR+=5.54	1.30–23.62	-	104
	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
	Sarno *et al.*[7]	Absence of BCG scar	OR=0.380	0.215–0.672	<0.001	-
	Düppre *et al.*[29]	Higher risk among unvaccinated	OR=1.8	8.3–4.6	0.03	2,135
	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
	Teixeira *et al.*[26]	Older than 50 years	aOR=3.11	2.03–4.76	-	4,509
	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
	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
	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
	Sales *et al.*[15]	Household contact (co-prevalents)	OR=1.33	1.02–1.73	-	6,158
	Sales *et al.*[15]	Household contact	OR=1.96	1.29–2.98	-	6,158
	Santos *et al.*[31]	Household contact	aOR=1.33	1.00–1.77	0.048	7,012
	Teixeira *et al.*[26]	Household contact	OR=1.48	1.17–1.88	-	42,725
Consanguinity/ Relationship	Durães *et al.*[27]	Consanguineous	OR=2.8	1.77–7.74	-	197
	Durães *et al.*[28]	First degree kinship	OR=2.42	1.75–3.35	<0.0001	1,040
	Sales *et al.*[15]	Consanguineous	OR=1.89	1.42–2.51	-	6,158
	Santos *et al.*[31]	Spouse, fiance and boyfriend/ girlfriend (prevalent)	aOR=1.25	0.74–2.11	-	7,012
	Santos *et al.*[31]	Parents (prevalent)	aOR=1.69	0.97–2.96	-	7,012
	Santos *et al.*[31]	Brother (prevalent)	aOR=2.75	1.65-4.57	<0.001	7,012
	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.*[31]	Other consanguine relatives (prevalent)	aOR=1.70	0.98–2.94	-	7,012
	Santos *et al.*[31]	Spouse, fiancé and partner (incidents)	RR=7.53	2.51–22.57	<0.001	6,831
	Santos *et al.*[31]	Uncle, nephew, cousin, grandfather, and grandson	aRR=3.71	1.24–11.06	0.0019	6,831
	Santos *et al.*[31]	Parents (incidents)	aRR=10.93	3.48–34.27	<0.001	6,831
	Santos *et al.*[31]	Brother (incidents)	aRR=7.03	2.41–20.46	<0.001	6,831
	Santos *et al.*[31]	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.*[15]	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.*[15]	Bacillary index greater than 3 compared to IC with BI 0	OR=4.07	2.73–6.09	-	6,158
	Sales *et al.*[15]	Bacillary index from one to three compared to IC with BI 0	OR=4.30	2.12–8.71	-	6,158
	Sales *et al.*[15]	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.*[31]	BI 0.1 to 3.0 (incidents)	aRR=3.68	1.99–6.82	<0.001	7,012
	Santos *et al.*[31]	BI >3 (incidents)	aRR=5.27	2.96–9.38	<0.001	7,012
	Santos *et al.*[31]	BI 0.1 to 3.0 (prevalent)	aRR=3.68	1.99–6.82	<0.001	6,831
	Santos *et al.*[31]	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	191–27.98	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]	MI 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; [a]Neural 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 scars[7,10,29]. They pointed out a 3.7 times higher risk for contacts without a scar[10], and a 1.8 times higher risk among unvaccinated contacts[7].

Four studies identified that the presence of a BCG vaccine scar was considered a protective factor for developing leprosy[8,10,24,31]. The presence of at least one BCG vaccine scar showed a 2.44 times greater protection against neural impairment in leprosy contacts[35].

Genetic factors

Consanguinity

Four studies have identified the association between illness and consanguinity[15,27,28,31]. 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)[35] and OR=1.89 (95% CI: 1.42-2.51)[15]. When the kinship is of the first degree, the chance of developing leprosy was OR=2.42 (95% CI: 1.75; 3.35)[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[31].

Mycobacterium leprae positive PCR

Two studies identified an association between the illness and a positive PCR[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[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)[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)[35].

Sociodemographic determinants

Age

Three studies identified the age of the contact as a risk factor associated with illness[25,26,34]. 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)[26], and also people older than 60 years old (HR=32.4; 95% CI: 3.6-290.3)[25].

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)[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[31].

Factors related to cohabitation

Four studies identified an association between illness and type of contact[15,26,28,31]. 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[28]; OR=1.96 (95% CI: 1.29-2.98) for incident cases[15], and OR=1.33 (95% CI: 1.02-1.73) for co-prevalent cases, which was in line with another study[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[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[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[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[15] and bacilloscopic index[15,31]. 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[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)[31]. 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-prevalent cases[15].

Combined risks

Two studies identified an association between BCG, ML Flow, Mitsuda test, and the development of leprosy among the contacts[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)[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[26].

Protective factors against illness in leprosy contacts

The protective factors against illness were the presence of one or more BCG vaccine scars[8,10,24,31,35], positive Mitsuda test[8] and the level of education of leprosy contacts[26]. The protection 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	Goulart *et al.*[10]	One or more BCG scars	72.9% – 0.27	0.13–0.59	-	1,396
	Santos *et al.*[31]	Presence of BCG scar	OR=0.30	0.22–0.41	-	7,174
	Santos *et al.*[31]	Presence of BCG scar	0.22-0.41	0.44–0.90	-	7,174
	Araújo *et al.*[8]	Two or more BCG scars	RR=0.0459	0.006–0.338	-	2,992
	Gomes *et al.*[24]	Two scars compared to no BCG scars	RR=0.41	0.2016–0.8319	p= 0.007	5,661
	Santos *et al.*[31]	One BCG scar	OR =0.41	0.18–0.98	p= 0.044	210
Positive Mitsuda Test	Araújo *et al.*[8]	Mitsuda reactions >7 mm compared to 0-3 mm reactions	RR= 0.1446	0.0566–0.3696	-	2,992
Education/ schooling	Teixeira *et al.*[26]	No schooling or preschool	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[37,38]. 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[3,39,40] and that illness among seropositive individuals can vary from 2 to 13%[4,8,10,29,41]. 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[42]. These data reinforce the importance of testing to monitor leprosy contacts[7].

The Mitsuda test helps with the diagnosis of leprosy[43], especially when combined with other tests, and can also be useful for monitoring household and social contacts of leprosy patients[44-46]. 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%[45,47,48] of healthy contacts, and the proportion of positive reactions may increase with age[44]. In a study with leprosy patients, the participation of the allele HLA-DQ1 in the absence of response to the Mitsuda test[49] has been reported. Then, new studies that investigate cellular immunity in leprosy contacts would contribute substantially to getting new biomarkers[39].

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[9,11]. A meta-analysis[9] 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[50].

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[11,50,51]. 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[7,8,39]. 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[52-54]. Genetic and/or environmental factors may exert a crucial influence on the transmission of *M. leprae* infection and/or the pathogenesis of leprosy[54]. 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[36], 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[37]. 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[14]. Social inequality increases the susceptibility to various diseases, including leprosy[13]. Another study reported an association between the development of leprosy and social conditions, even though these associations would not necessarily imply a causal connection[16] corroborating the findings of this review. Education level has been reported as a risk[31] and protective[26] factor. Several studies pointed to a higher chance of getting sick with leprosy in the lower economic class population[14,16,55].

An integrative review[56] 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[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[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[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[58].

This study described the scientific evidence related to the development of leprosy in Brazilian contacts by synthetizing 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.

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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.

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