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Factors associated with the development of leprosy in contacts: a systematic review and meta-analysis

Fatores associados ao adoecimento por hanseníase em contatos: revisão sistemática e metanálise

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ABSTRACT: ***Objective*:** To investigate the risk factors associated with leprosy in contacts of patients. ***Method*:** We carried out a systematic review and meta-analysis by searching the databases MEDLINE, Embase, Cochrane Library, CINAHL, LILACS, Scopus, and Web of Science until September 2019. Four reviewers carried out the selection, analysis, and evaluation of quality of studies. The random effects model was used to calculate the pooled relative risk (RR) and 95% confidence intervals (95% CI) when heterogeneity was greater than 50%. ***Results*:** The search resulted in 2,148 references and included 24 reports. Most of the studies had been conducted in Brazil and India, had a cohort design and included household, neighbors, and social contacts. The risk factors associated with illness due to leprosy in contacts were: illiteracy (RR = 1,48; 95%CI 1,22 – 1,79), living in the same house (RR = 2,41; 95%CI 1,87 – 3,10) of a case of leprosy with high bacillary load (RR = 2.40; 95%CI 1.69 – 3.41), seropositivity to the *Mycobacterium leprae* PGL-1 (phenolic glycolipid-1) antigen (RR = 3.54; 95%CI 2.21 – 5.67), presence of the bacillus in the bloodstream (RR = 10.61; 95%CI 4.74 – 23.77) and negative Mitsuda reaction (RR = 2,68; 95%CI 1,76 – 4,07). Immunization with BCG (bacillus Calmette-Guérin) vaccine had a protective effect against leprosy. ***Conclusion*:** Leprosy in contacts of patients involves social determination, individual susceptibility, and difficulties in access to disease control actions, but modifiable risk factors are the main determinants of illness in this population.

***Keywords*:** Leprosy. Risk factors. Social determinants of health. Epidemiological monitoring. Systematic review. Meta-analysis.

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RESUMO: ***Objetivo***: Investigar os fatores de risco associados ao adoecimento por hanseníase em contatos de casos da doença. ***Métodos*:** Realizou-se uma revisão sistemática e metanálise com busca nas bases de dados: *Medical Literature Analysis and Retrieval System Online* (MEDLINE), Embase, Cochrane Library, *Cumulative Index to Nursing and Allied Health Literature* (CINAHL), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Scopus e *Web of Science* até setembro de 2019. A seleção, a análise e a avaliação da qualidade dos estudos foram realizadas por quatro revisores. Utilizou-se modelo de efeitos aleatórios para calcular o risco relativo agrupado (RR) e intervalos de confiança de 95% (IC95%) quando na presença de heterogeneidade superior a 50%. ***Resultados*:** A busca resultou em 2.148 referências e foram incluídos 24 estudos. Estes, em sua maioria, foram realizados no Brasil e na Índia, com delineamento coorte, e incluíram contatos domiciliares, peridomiciliares e sociais. Mostraram-se associados ao adoecimento por hanseníase em contatos: o analfabetismo (RR = 1,48; IC95% 1,22 – 1,79), a convivência intradomiciliar (RR = 2,41; IC95% 1,87 – 3,10) com caso de hanseníase apresentando alta carga bacilar (RR = 2,40; IC95% 1,69 – 3,41), a soropositividade ao antígeno PGL-1(glicolipídeo fenólico-1) do *Mycobacterium leprae* (RR = 3,54; IC95% 2,21 – 5,67), presença do bacilo na corrente sanguínea (RR = 10,61; IC95% 4,74 – 23,77) e reação de Mitsuda negativa (RR = 2,68; IC95% 1,76 – 4,07). A imunização com bacilo Calmette-Guérin (BCG) teve efeito protetor contra o adoecimento (RR = 0,52; IC95% 0,34 – 0,78). ***Conclusão*:** O adoecimento por hanseníase em contatos perpassa pela determinação social, pela susceptibilidade individual e por fragilidades no acesso às ações de controle da doença; contudo, fatores de risco modificáveis são os principais determinantes do adoecimento nessa população.

***Palavras-chave*:** Hanseníase. Fatores de risco. Determinantes sociais da saúde. Monitoramento epidemiológico. Revisão sistemática. Metanálise.

INTRODUCTION

Leprosy is a chronic infectious disease caused by the bacillus *Mycobacterium leprae* (*M. leprae*). In 30 years of multidrug therapy, cases increased from more than 5 million annually to less than 200,000 in 2014[1]. This goal of less than one case per 10,000 inhabitants was reached by most countries in 2005; however, even nowadays, the elimination of leprosy remains a challenge in several countries[2].

In 2017, 210,671 new cases of leprosy were diagnosed globally[3]. As control strategies, the treatment of patients, early diagnosis and surveillance of contacts contributed to the decrease in incidence[4]. However, there was an increase in prevalence across the world in 2017 compared to the previous year, with 20,765 more cases[3]. The challenges of leprosy control include continued transmission of the bacillus, difficulties in surveillance of contacts, and limited knowledge about transmission[5]. The prevention of leprosy requires interventions with emphasis on patient contacts[6] since contact is the main determinant for the lingering of incidence levels[7].

Studies have shown different dimensions of risk for the illness of people who got in contact with leprosy cases, enabling the monitoring of the effects of predictive variables[8,9]. Systematic reviews on this theme are scarce and mostly address subclinical infection markers and the use of chemoprophylaxis to prevent the disease[10,11]. This study, therefore,

intends to advance the discussion of the dimensions of risk for leprosy by incorporating current findings and contributing to establishing the profile of the individual, social and epidemiological characteristics that make contact groups vulnerable to this disease.

Leprosy-control policies reinforce the need for the systematic detection of contacts to identify those at higher risk of becoming ill[5]. A more comprehensive understanding of factors that lead to individual vulnerability is needed. Thus, the aim of this study was to investigate the risk factors associated with the development of leprosy among contacts of patients.

METHODS

The protocol of this systematic review and meta-analysis was registered in the platform International Prospective Register of Systematic Reviews (PROSPERO) under the code CRD42019148528, and the report followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The following databases were searched between August and September 2019: Medical Literature Analysis and Retrieval System Online (MEDLINE), via PubMed, Embase, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Latino- American and Caribbean Health Sciences (LILACS), via the Virtual Health Library (VHL), Scopus and Web of Science.

The outcome investigated was clinical diagnosis of leprosy performed by a specialized professional in reference services or another health unit. "Contacts" were defined as individuals who lived with a person affected by leprosy in the same household or social environment at the time of diagnosis or in a previous period. In order to define the search terms, the controlled vocabularies Health Sciences Descriptors (DeCS), Medical Subject Headings (MeSH), and Embase Subject Headings (EMTREE) were consulted. Significant free terms were also included (Supplementary Material 1). No language or publication date/period filters were applied.

Studies published in full text, with a cohort, case-control, or cross-sectional design that included leprosy as an outcome and the use of measures of effect were included. Gray-literature productions were excluded, except for theses and dissertations, duplicates, qualitative review studies or meta-analyses, case reports, clinical trials, experimental studies, ecological studies, exclusively descriptive studies, and studies with no "contact" in the sample.

DATA COLLECTION AND ANALYSIS

The results were added up and duplicates were removed. The screening was performed by reading the title and abstract, followed by confirmation of eligibility by reading the full text by a pair of reviewers (ENAN and ICB; EOA and APMC) and independently. The information obtained was compared and any disagreements were resolved by consensus or

a third reviewer. The Kappa statistical test identified significant agreement in the decision-making process of the pair of reviewers (kappa = 0.39; p = 0.005 and kappa = 0.74; p < 0.0001, respectively). The programs Rayyan QCRI (Qatar Computing Research Institute) and Mendeley were used to manage the references.

The following information was extracted from the eligible studies and added to a standardized table: authors, year of publication, journal, location and period of study, design, sample, contact characteristic, comparison group (if any), outcome, risk factors, and measures of effect, recorded with a 95% confidence interval (95%CI) and p-value, when available. For the systematic review, information was aggregated to allow descriptive synthesis and categorization of variables into three dimensions of risk factors: social determinants, genetic susceptibility, and characteristics of exposure to *M. leprae*.

For the meta-analysis, only cohort studies were included. A random-effects model was used in the presence of heterogeneity ($I^2 \geq 50\%$) and a fixed-effects model for heterogeneity below 50%. In studies that evaluated chemoprophylaxis, data from the placebo group were used. Surveys with overlapping samples, lack of stratified information, or categories that made comparisons impossible were excluded. In these cases, the results were presented in the systematic review.

We present the relative risks (RR) and 95%CI, using the Mantel-Haenszel method and assuming a p-value < 0.05 as significant. The results were grouped in a forest plot. Publication bias was assessed using a funnel plot. Heterogeneity between studies was assessed using the I^2 statistic analysis, defining values < 25% as low heterogeneity, 25–50% as acceptable, and > 50% as high heterogeneity. Sensitivity analyses were based on the RR variation. The meta-analysis was conducted in the software Review Manager, version 5.4.1. The quality of work and the risk of bias were assessed using the Newcastle – Ottawa Quality Assessment Scale (NOS)[12], specific for the evaluation of non-randomized studies. The instrument has three categories: selection, comparability, and exposure, totaling eight questions. Among possible answers, a star can be assigned to the one that defines the least possibility of bias. In the end, the responses with nine stars at most are added up. Studies with ≥ 7 stars are considered to have a low risk of bias and those with < 7 stars, a high risk of bias.

RESULTS

A total of 2,148 references were screened, 103 papers were selected for full reading and 23 were considered eligible. Additionally, we included a study present in the Theses Repository of Universidade Federal de Minas Gerais, Brazil. Figure 1 shows the selection process.

Of the 24 publications, 23 were cohort studies and one was a cross-sectional study. The follow-up period ranged from one to twenty years (Supplementary Material 2), the publication covered the period from 1991 to 2019 and the most frequent language was English, followed by Portuguese. Brazil and India were the most represented countries.

The sample ranged from 68 to 28,092 participants. The contact categories were household, intra-household, neighbors, relatives, and social. The incidence of leprosy in contacts ranged from 0.21 to 21.7%, being lower in Venezuela and higher in Brazil.

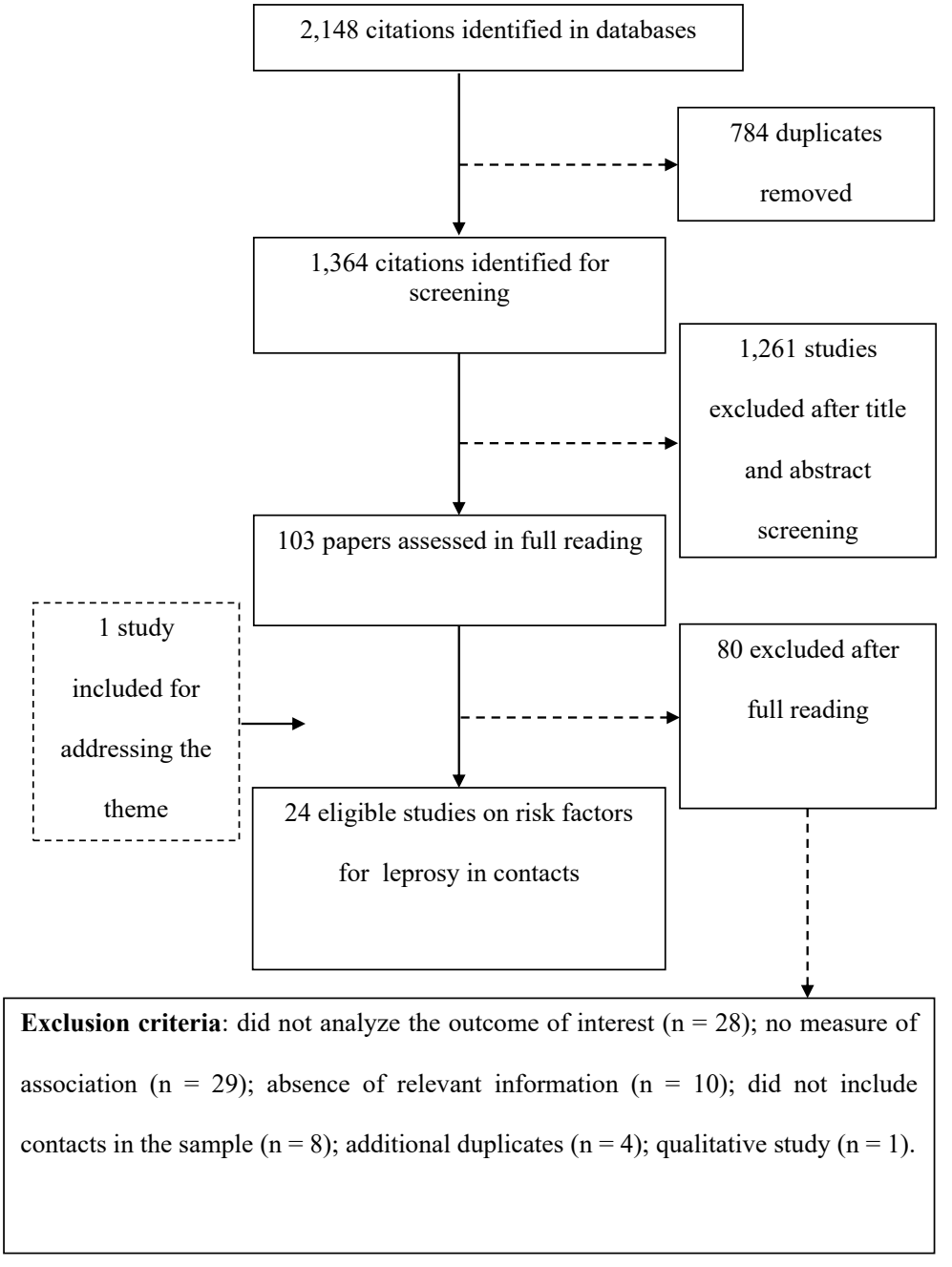

Figure 1. Selection process of eligible studies to compose the systematic review.

Risk factors are described in Supplementary Material 3. The excluded studies are presented in Supplementary Material 4.

The scores of study quality and risk of bias ranged from six to nine stars. Nineteen cohorts (79%) scored ≥ 7, indicating a low risk of bias. Sources of bias were associated with loss to follow-up and difficulties in comparisons between groups due to non-matching or lack of adjustment for confounding variables. The cross-sectional study was not evaluated due to the absence of a standardized questionnaire in the NOS instrument.

DOMAIN 1: SOCIAL DETERMINANTS

This domain included: sex, age, housing, income, and education. Sex and age were evaluated in seven cohort studies[13-19]. Two studies reported a lower incidence of leprosy in children under five years of age[13,14]. Ages from 15 to 19 years old and over 30 years old were associated with leprosy[15]. The association of sex with the disease showed conflicting results[13-17]. The meta-analysis did not find a statistically significant association of these variables with the condition, with significant heterogeneity in studies that assessed gender ($I^2 = 92\%$) (Figures 2A and 2B).

The relationship between family size and leprosy was investigated in two studies; one of them compared groups of contacts, finding no association[13]; the other compared contacts and non-contacts and reported a higher risk between contacts living in environments with a greater number of people (hazard ratio = 3.47; p = 0.003)[14]. Lower-income was not associated with the development of leprosy in contacts in an Indian study[13]. On the other hand, in Brazil, contacts with a monthly income of less than three minimum wages had a greater chance of becoming ill, even when the family income of the leprosy case was analyzed[16]. Two studies assessed schooling[13,16]; only one reported a higher risk of leprosy among people with less education[16]. Differences in categorization made the meta-analysis of housing and income impossible. The meta-analysis of schooling showed a higher risk of leprosy in illiterate contacts (RR = 1.48; 95%CI 1.22 – 1.79; p < 0.0001) (Figure 2C).

DOMAIN 2: GENETIC SUSCEPTIBILITY

This domain included consanguinity, evaluated in four studies[15,16,20,21]. All papers reported a significantly higher chance of leprosy in consanguineous contacts, especially first-degree relatives[15,16,20,21]. This association remained significant in the adjusted analyses[15,16,20]. Second-degree relative or other kinship was not associated with the development of leprosy; however, one study reported a higher risk among spouses (odds ratio = 3.29; 95%CI 1.56 – 6.96)[15]. Only two papers were included in the meta-analysis[16,20]. There was a higher risk of leprosy development in consanguineous contacts, however, the association was borderline (RR = 1.32; 95%CI 0.98 – 1.78; p = 0.07) (Figure 2D).

DOMAIN 3: EXPOSURE TO *MYCOBACTERIUM LEPRAE*

This domain included aspects of living with the leprosy patient and immune responses triggered by exposure to the bacillus. Aspects of living with the patient included contact characteristics and clinical characteristics of the case. As for the characteristics of the contact, the most frequent variable was the type of contact included in nine studies[14-18,20,22,24]. Eight reported a higher risk of leprosy development in household contacts[14,16-18,20,22-24].

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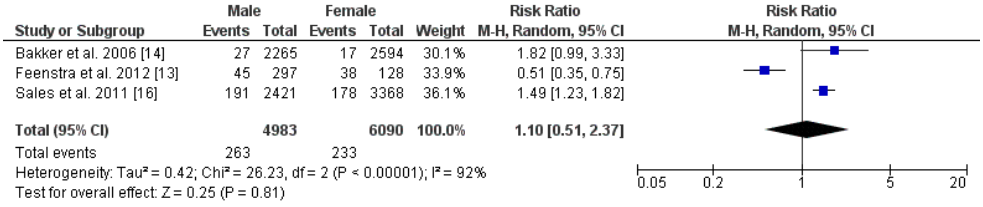

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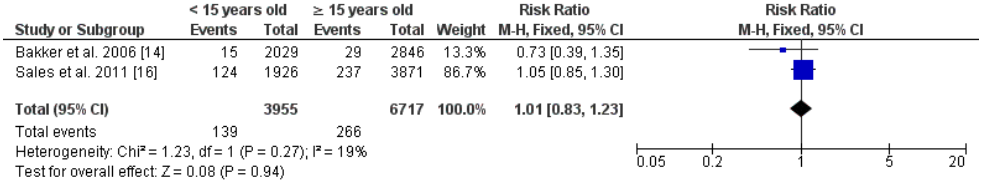

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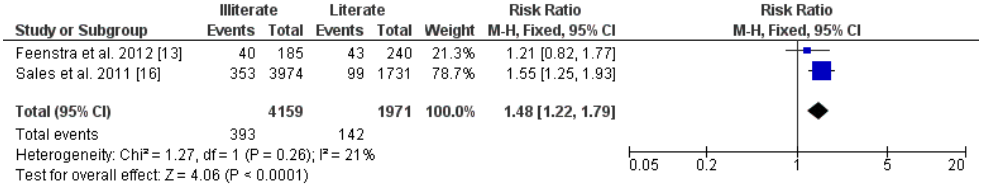

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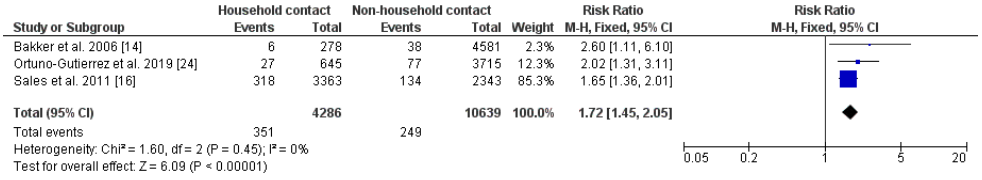
Figure 2. Forest plot of meta-analysis of social determinants and genetic susceptibility associated with the development of leprosy in contacts. (A) Sex. (B) Age. (C) Education. (D) Blood relationship with a leprosy patient.

In the meta-analysis, household contact was a risk factor for the disease when compared with individuals without contact (RR = 1.72; 95%CI 1.45 – 2.05; p < 0.00001) and also with neighbors of leprosy patients (RR = 2.41; 95%CI 1.87 – 3.10; p < 0.00001) (Figures 3A and 3B). The physical distance from a patient was evaluated in three investigations[14,15,24]. A physical distance ≤ 25 meters was related to a greater chance of leprosy development in studies in India[15] and Comoros[24], although in Indonesia no significant association was found[14].

a)



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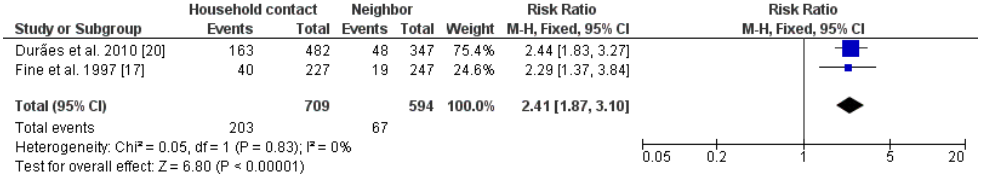

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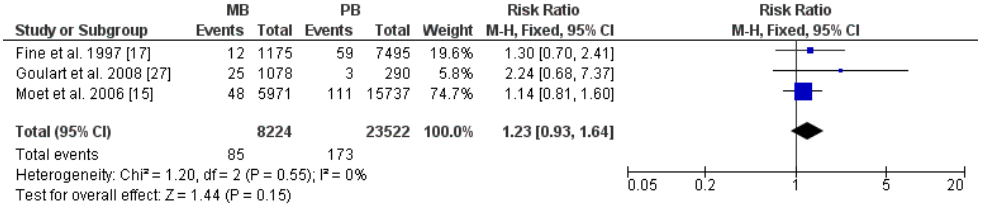

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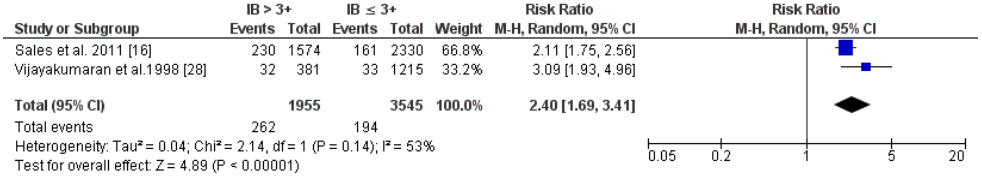

Figure 3. Forest plot of the meta-analysis on the characteristics of living with a leprosy patient and the risk of becoming ill in contacts. (A) Household contact compared to individuals without contact. (B) Household contact compared to neighbors. (C) Leprosy classification of the case. (D) Bacilloscopic index of the case.

Living with leprosy cases for at least five years increased the chance of becoming ill by two times[16]. A higher risk was also reported in unvaccinated contacts who lived with cases for a period equal to or greater than 21 years[18]. Living with more than one patient increased the chance of becoming ill in contacts from two to six times[13,14,25], even in those who received chemoprophylaxis with a dose of rifampicin[13]. The clinical characteristics of the patients were evaluated in nine studies[14-19,26-28]. Of these, eight reported a higher risk of leprosy in contacts of patients with multibacillary forms (MB)[14,15,17,19,26-28], especially household contacts younger than 15 years[17]. Two studies found a greater chance of leprosy among contacts of paucibacillary cases (PB)[17,19]. The meta-analysis showed that there was a greater risk among contacts of MB cases compared to PB cases, but this association was not statistically significant (RR = 1.23; 95%CI 0.93 – 1.64) (Figure 3C).

Four studies reported a greater chance of leprosy in contacts of patients with positive bacilloscopic index (BI)[14,16,18,28]. Contacts of patients with BI > 2+ had three times the risk of becoming ill[16,28]. This risk increased from four to seven times for contacts of patients with BI > 3+[16]. Contacts of families whose sum of BI was > 3.6 also had a higher risk of developing the disease, regardless of immunization with bacillus Calmette-Guérin (BCG)[18]. The meta-analysis showed that contacts of patients with BI > 3+ had a higher risk of becoming ill (RR = 2.40; 95%CI 1.69 – 3.41; $p < 0.0001$), however heterogeneity between studies was high ($I^2 = 53\%$) (Figure 3D). Living with patients presenting physical disabilities increased the chance of leprosy in contacts by almost ten times[14,16].

Eight cohorts analyzed BCG vaccination as an interaction factor and in adjusted analyses,[14-18,26,27,29], but only Brazilian studies reported a significant reduction in the chance of developing the disease[16,26,27,29]. Studies conducted in Indonesia, India, Malawi, and some in Brazil did not report a significant association[14,15,17,18]. In the meta-analysis, the presence of a vaccine scar was associated with protection against leprosy in contacts (OR = 0.52; 95%CI 0.34 – 0.78; $p = 0.002$) (Figure 4A). Selecting works from different countries resulted in a significant heterogeneity ($I^2 = 78\%$). In the sensitivity analysis that included only Brazilian studies[16,26,29], the association remained significant (RR = 0.40; 95%CI 0.30 – 0.54), with high heterogeneity ($I^2 = 57\%$).

Seropositivity to *M. leprae* antigens was addressed in 15 papers[14,18,19,22,23,25,27,29-36]. Eleven studies reported a significant increase in the risk of leprosy in contacts with anti-PGL-1 (anti-phenolic glycolipid- 1) seropositivity[14,18,22,25,27,29-34], even in children under fifteen years of age[36]. The meta-analysis found that the risk of leprosy in contacts with positive anti-PGL-1 serology was significantly higher compared to contacts with negative serology (RR = 3.54; 95%CI 2.21 – 5.67; $p < 0.0001$) (Figure 4B). However, the analysis with all studies revealed significant heterogeneity ($I^2 = 78\%$).

Due to the use of different serological analysis methods, it was decided to perform a sensitivity analysis that would restrict the meta-analysis to studies that used the Enzyme-Linked Immunosorbent Assay (ELISA) technique, with a cut-off point lower than 0.3. This resulted in five papers[14,23,25,31,35]. After adjustment, the association of anti-PGL-1 seropositivity with the illness of contacts remained significant (RR = 2.41; 95%CI 1.62 – 3.59) and

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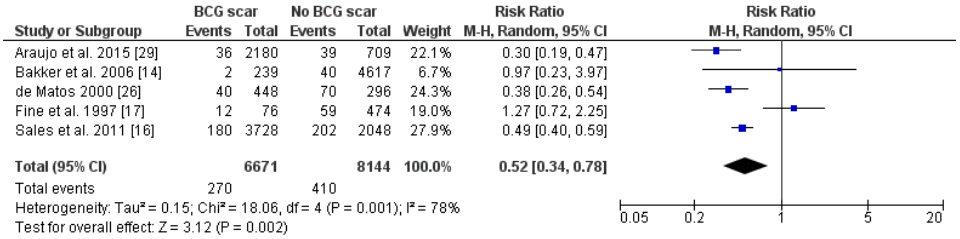

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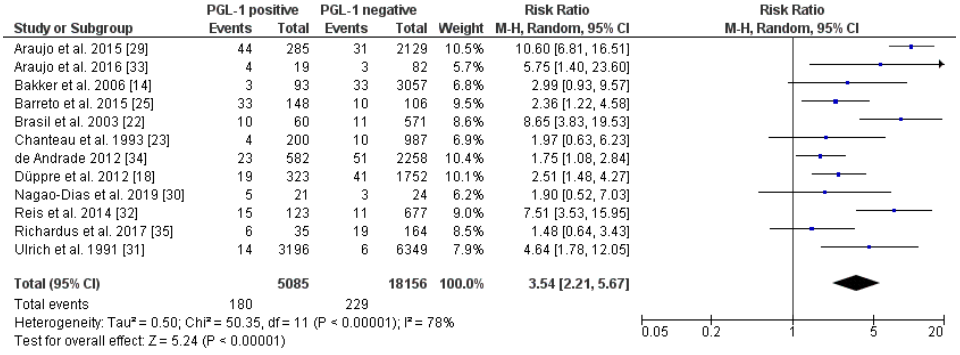

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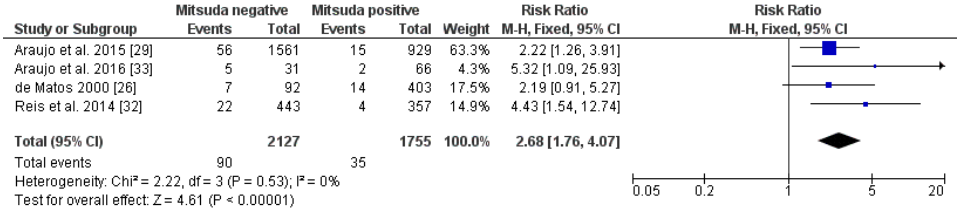

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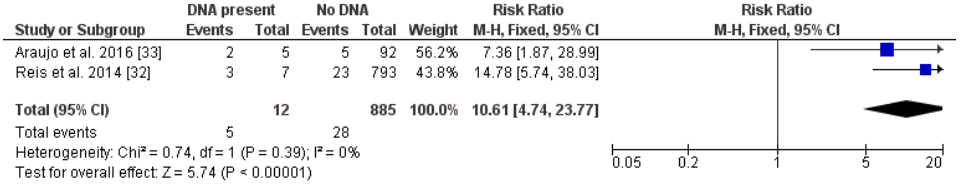

Figure 4. Forest plot of meta-analysis on the characteristics of the immune response and the risk of leprosy in contacts. (A) Calmette-Guérin bacillus vaccine scar. (B) Anti-phenolic glycolipid-1 serology. (C) Reaction to Mitsuda Test. (D) Deoxyribonucleic acid of *M. leprae* in the bloodstream.

with no heterogeneity ($I^2 = 0\%$). A similar result was observed when studies that assessed serology using the ML Flow test were included[22,34] (RR = 2.06; 95%CI 1.44 – 2.95; $I^2 = 0\%$).

Five studies analyzed the Mitsuda reaction in contacts[26,27,29,32,33]. A positive reaction was associated with protection against the disease[27,29,32], and the reaction < 7 mm, along with anti-PGL-1 seropositivity, was proven to be a risk factor[26,29]. The pooled estimates showed a higher risk of leprosy in contacts with a negative reaction (RR = 2.68; 95%CI 1.76 – 4.07; $p < 0.0001$) (Figure 4C).

The presence of bacillary deoxyribonucleic acid (DNA) in the nasal mucosa of contacts increased the risk of leprosy[33], being 14 times higher when present in the bloodstream[32,33]. Living with patients that presented bacillary DNA in the nasal mucosa was also a risk factor[14]. The meta-analysis showed that contacts with bacillus DNA in the bloodstream had a higher risk of developing leprosy (OR = 10.61; 95%CI 4.74 – 23.77; $p < 0.0001$). However, the studies were conducted at the same reference center, which suggests the possibility of sample overlap and overestimation of the pooled statistics.

Sensitivity analysis in studies with a low risk of bias showed no differences in pooled statistics. Visual inspection via funnel plot of all studies showed asymmetry, suggesting a risk of publication bias (Supplementary Material 5). The presence of a void in the lower-left portion of the funnel suggests that smaller studies that evaluated variables associated with protection may not have been published.

DISCUSSION

The systematic review showed a higher risk of leprosy among contacts who were young and adults, who lived with patients in crowded households, had lower income and low education. The meta-analysis confirmed the greatest risk for illiterate contacts.

The incidence of leprosy among young people indicates early exposure to *M. leprae*. The disease's incubation period lasts, on average, five years[27], which is why the illness in young people denotes continued transmission of the bacillus. Households with a greater density of residents facilitate transmission through close contact[14]. Systematic reviews and meta-analysis studies reported a greater chance of leprosy among individuals with worse housing conditions, low education, the experience of scarcity or reduction in the variety of foods, unemployment, and lower income. These conditions also contributed to severe physical disabilities, impaired social participation, and worsened quality of life[37,38]. Brazil, India, and Indonesia are the countries with the highest leprosy burden in the world[3] and have a significant portion of their populations living with extreme difficulty in accessing minimal resources for survival[39]. The persistence of poverty, social inequality, and gaps in addressing social determinants are the main challenges in eliminating leprosy. Vulnerable populations commonly face barriers to accessing state goods and services, including access to early diagnosis of leprosy, timely treatment, and management of physical disabilities[40].

The systematic review and meta-analysis showed conflicting results of the risk of becoming ill according to the sex of contacts. In the adult population, a lower proportion of leprosy notifications is observed among females, while in children this distribution is usually the same between sexes[5]. Differences can be explained by the influence of gender on access to health care, cultural factors, restrictions on women's social participation, and physiological differences associated with the risk of or protection against leprosy[5,13,17].

Consanguinity was repeatedly reported as a risk factor for leprosy in contacts; the meta-analysis, however, did not show a significant association. The number of studies included and their heterogeneity influenced the significance of the analysis. The risk of leprosy seems to depend on the individual's genetic background[41]. Genetic susceptibility to leprosy involves genes that encode functional products involved in immunological pathways[42], such as lymphotoxin-α[43], parkin (PARK2), and parkin coregulated gene (PACRG)[44], interleukin 10 (IL-10)[45], interferon-gamma (IFN- γ)[46] and pattern recognition receptor (PRR) genes[47,48]. The genetic architecture of leprosy is still not well understood. Further studies are needed to clarify the share of the risk attributable to genetics in the susceptibility to leprosy.

Household contact was an important risk factor for leprosy. A survey showed that contact surveillance linked 28% of incident cases to a source of intra-household transmission and 36% to transmission in the neighborhood. The inclusion of social contacts would allow identifying 15% more incident cases[7], reinforcing that the inclusion of social contacts in surveillance allows for greater coverage in the detection of individuals at risk.

There was also a significant risk of leprosy among contacts of high BI cases. Operational difficulties of health services, reflected by the presence of undiagnosed multibacillary patients, the increase in the number of cases in the dwelling environment, and the evolution to physical disabilities, impact the risk of illness in contacts[14,17]. To achieve the goals of reducing the burden of leprosy in priority countries, specific strategies may not be enough to reduce the risk of this illness in vulnerable populations. Access to universal health coverage and the strengthening of leprosy control actions are rather necessary.

Bacillus antigens seropositivity, the presence of bacillary DNA in the airways and bloodstream, and a negative response to the Mitsuda test were also risk factors for leprosy in contacts. The positive reaction to the Mitsuda test indicates a predominance of the cellular immune response, resulting in a protective effect of acquired immunity[27]. Bacillary DNA in the airways and/or bloodstream indicates passage of the bacillus through the upper respiratory tract, colonization of macrophages, and passage of the phagocytosed bacillus by immune system cells towards more favorable sites, such as skin and peripheral nerves[27,32]. The presence of bacillary DNA in biological samples and seropositivity for bacillus antigens suggests subclinical infection in contacts, making them more prone to developing the disease[27,32,33].

M. leprae antigens seropositivity is a biomarker of infection at the individual level[25], indicating a potential source of transmission, the need for greater surveillance and, possibly, the use of chemoprophylaxis[14]. However, as a result of the low sensitivity of the tests, the applicability for early detection of cases is still uncertain and seronegative contacts should not be neglected[18,25].

The evaluation of the effect of the BCG vaccine had conflicting results because of the high heterogeneity between studies, possibly due to differences in methodology and related to the setting in which the research was conducted. BCG acts on the immune system by increasing *M. leprae*-responsive T cells and the production of inflammatory mediators[49]. Leprosy control policies in Brazil recommend that household contacts without signs suggestive of the disease be immunized with an additional dose of BCG[4]. Thus, the results of Brazilian studies may be related to the extensive policy of immunization with BCG in childhood and the revaccination of contacts in the country.

Given the multidimensionality and complexity of the interaction between risk factors, the limitations of this study include isolated and punctual analysis, which makes it impossible to assess the relationship between factors jointly, and the comparability between studies from countries that diverge from each other in socioeconomic issues, in the endemicity of leprosy and in the access to health care. The small number of studies included in the analysis of each risk factor, heterogeneity, and the possibility of publication bias are limitations of the meta-analysis.

The risk of becoming ill from contacts permeates social vulnerability, individual susceptibility, and difficulties in accessing health services. Despite the influence of immune responses on disease susceptibility, modifiable risk factors seem to be the main determinants of illness from leprosy among contacts.

A comprehensive analysis of risk factors for leprosy can contribute to improving the surveillance of contacts by health professionals, enabling the application of this knowledge in instruments that allow the stratification of individual risk. Evidence shows that the reduction of leprosy burden involves identifying vulnerable groups and requires intersectoral coordination to ensure access to policies for social inclusion, education, income and the promotion of equity in access to health services, in addition to strengthening the leprosy control activities.

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