Indian J Lepr 2018, 90 : 217-234

http://www.ijl.org.in

Review Article

Chemoprophylaxis for Contacts of Leprosy Patients: A Systematic Review and Meta-analysis

[1, 2]APM Ferreira, [1]W Fan, [3]A Agarwal, [2]MCL Virmond, [2]NGA Galan, [1]RAMB Almeida, [1]EC Jorge, [2]OS Rosa, [1,4,5]R ElDib

Received : 26.01.2018 Accepted : 30.06.2018

Individuals who are in close association or proximity with leprosy patients have a greater chance of acquiring the disease. However, the effectiveness of chemoprophylaxis in preventing leprosy in contacts of affected patients for optimal disease control remains unclear and a significant public health issue in developing countries such as India, Brazil, and Bangladesh. Electronic searches of Medline, EMBASE, CENTRAL, and LILACS up to October 2017 were conducted to identify eligible studies. Reference lists of potentially eligible studies were reviewed. We included randomized controlled trials (RCTs) comparing chemoprophylaxis with placebo for the prevention of leprosy infection in contacts of affected patients. A pair of reviewers independently screened eligible articles, extracted data, and assessed risk of bias. The GRADE approach was used to rate overall certainty of the evidence. Six RCTs including 52,483 participants proved eligible. Results suggested a statistically significantly reduction in clinical leprosy in contacts both, up to two years (Risk Ratio (RR) 0.32, 95% Confidential Interval (CI) 0.17, 0.62; $p < 0.0007$; I^2=70%, p=0.07; low-certainty evidence) and from two to five years of follow-up (RR 0.51, 95% CI 0.29, 0.89; p=0.02; I^2=80%, $p < 0.0005$; low-certainty evidence) with the use of chemoprophylaxis in comparison to placebo. However, results suggested a non-significant reduction in clinical leprosy in contacts over five years (RR 0.77, 95% CI 0.46, 1.28; p =0.31; I^2=48%, p=0.16; low-certainty evidence). Low-certainty evidence shows that chemoprophylaxis is effective in the reduction of clinical leprosy in contacts up to two years and from two to five years. However, due to low-certainty evidence there is no significant effect of chemoprophylaxis in contacts, over five years follow-up period.

Keywords: chemoprophylaxis; leprosy; GRADE; systematic review; meta-analysis.

[1] Botucatu Medical School, Universidade Estadual Paulista, São Paulo, Brazil.

[2] Lauro de Souza Lima Institute, Bauru, Brazil.

[3] School of Medicine, University of Toronto, Toronto, Ontario, Canada.

[4] Institute of Science and Technology, Department of Biosciences and Oral Diagnosis, Universidade Estadual Paulista, São José dos Campos, Brazil.

[5] McMaster Institute of Urology, McMaster University, Ontario, Canada.

Corresponding author: Ana Paula do Prado Marques Ferreira

Lauro de Souza Lima Institute - Rehabilitation Department, Rod. CMTE João Ribeiro de Barros, Km. 225/226. Bauru, São Paulo - Brazil. Zip Code 17034-971, **E-mail:** pradofisio@hotmail.com

Background

Leprosy, also known as Hansen's disease, is an infectious chronic disease caused by *Mycobacterium leprae*, an acid-fast rod-shaped bacillus. Common disease manifestations include skin lesions and peripheral neuropathy, resulting in impaired pain sensation and physical disabilities often affecting the extremities (Scollard et al 2006).

More than three million persons are affected by leprosy worldwide (WHO 2005). Disease burden is greatest in developing countries like India, Brazil, Indonesia, Bangladesh, the Democratic Republic of Congo, and Ethiopia. Newly-detected cases globally indicate a marginal increase from 210,758 in 2015, to 214,783 in 2016, of which 12,819 have grade II disabilities (i.e., loss of protective sensation and visible deformities) (WHO 2017).

Individuals in close contact with or close proximity to leprosy patients have a greater chance of acquiring the disease. Hence, person-to-person transmission remains a significant public health concern, and household contacts are at high risk of disease transmission (Smith and Aerts 2014). In the absence of an effective vaccine, disease prevention relies largely on early and adequate treatment of diagnosed cases, surveillance for household and social contacts of affected patients, and prophylactic strategies for these contacts. In particular, contacts who are living with or have lived with leprosy patients in the past five years are at particularly high risk and must be carefully monitored and managed (Moet et al 2008, Ministério da Saúde 2016). Multi-drug chemotherapy with Rifampicin, Dapsone and Clofazimine (multidrug treatment, MDT) is the primary therapeutic strategy for cure of leprosy (Ministério da Saúde 2016).

To prevent leprosy transmission, some studies suggest that chemoprophylaxis combined with Bacillus Calmette–Guérin (BCG) vaccine may be a promising strategy for the future control of leprosy (Richardus and Oskam 2015, Cunha et al 2010).

Two previous systematic reviews have been conducted examining chemoprophylaxis for leprosy prevention (Smith and Smith 2000, Bhalla 2008). However, these reviews presented several limitations, including searching limited health databases, being restricted to English-language studies, or only including randomized controlled trials (RCTs) conducted in India (Smith and Smith 2000, Bhalla 2008). A more recent systematic review (Reveiz et al 2009) evaluating chemoprophylaxis for leprosy prevention among contacts of newly-diagnosed patients has been published, but failed to include Feenstra et al 2012, a landmark RCT with 21,711 participants. Another recent systematic review on the topic considered a number of study designs as eligible but was limited to the evaluation of rifampicin only, did not include an electronic search of EMBASE, involved language restrictions, and did not include a quantitative meta-analysis (Ferreira et al 2017).

In light of these major limitations in previous reviews, we undertook a systematic review of RCTs evaluating patient-important outcomes with chemoprophylaxis for the prevention of leprosy in contacts of affected patients.

Methods

This review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement (Moher et al 2009).

Eligibility criteria : We included *randomized controlled trials (RCTs)* and quasi-RCTs that compared chemoprophylaxis alone (e.g., Rifampicin, Dapsone, Acedapsone) with placebo, no intervention, BCG vaccine alone, or combination

therapy (e.g. Rifampicin and BCG vaccine) in contacts of patients with leprosy (i.e., household and social). Studies reporting one or more of the following patient-important outcomes were considered eligible: development of clinical leprosy in contacts of patients with leprosy and adverse events associated with chemoprophylaxis.

Data source and searches : We searched the following electronic databases up to October 23th, 2017: Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, issue 10, 2017); Medical Literature Analysis and Retrieval System Online (MEDLINE; 1966 to October 2017); Excerpta Medica database (EMBASE; 1980 to October 2017); Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS; 1982 to October 2017); and clinicaltrials.gov. The databases were searched using a comprehensive search strategy for RCTs and quasi-RCTs, along with MeSH (Medical Subject Headings) and text-words, including the following: leprosy, Hansen's disease, chemoprophylaxis, BCG (Appendix Table 1).

The reference lists of identified review articles were also screened for eligible trials. References of the relevant studies were also screened for eligible studies. Content experts were contacted to identify additional studies.

Title, abstract and full-text screening was conducted by paired reviewers independently. Conflicts were resolved via discussion, with third party adjudication as necessary.

Data extraction and risk of bias assessment : Paired reviewers (APMF and WF) independently extracted the following data using a pre-standardized data extraction form: characteristics of the study design; participants; interventions; outcomes event rates; and follow-up duration. Conflicts were resolved via discussion, with third party (RED and MCLV) adjudication as necessary. Where necessary, authors were contacted for additional data for eligible studies.

Paired reviewers independently assessed risk of bias using a modified version of the Cochrane Collaboration's tool for assessing risk for bias tool (Higgins et al 2011) (http:/distillercer.com/resources/) that included nine domains:

Appendix Table 1 : Search strategy

(chemoprophylaxis OR Chemoprevention OR chemoprohylactic prevention OR chemoprohylactic strategies OR chemoprohylactic strategy OR Rifampin or Benemycin or Rifampicin or Rimactan or Tubocin or Rifadin or Rimactane or Sulfonyldianiline OR Diaminodiphenylsulfone OR Diaphenylsulfone OR 4,4'-Diaminophenyl Sulfone OR 4,4' Diaminophenyl Sulfone OR Sulfone, 4,4'-Diaminophenyl OR DADPS OR Sulfona OR Orsade Brand of Dapsone OR Dapson-Fatol OR Fatol Brand of Dapsone OR Disulone OR Avlosulfone OR Dapsoderm-X OR Mex-America Brand of Dapsone OR Ofloxacine OR DR-3355 OR DR 3355 OR DR3355 OR Hoe-280 OR Hoe 280 OR Hoe280 OR ORF-28489 OR ORF 28489 OR ORF28489 OR Ru-43280 OR Ru 43280 OR Ru43280 OR Tarivid OR DL-8280 OR DL 8280 OR DL8280 OR Ofloxacin Hydrochloride OR Ofloxacin OR Acedapsone OR 4,4'-Diacetyldiaminodiphenylsulfone OR 4,4' Diacetyldiaminodiphenylsulfone OR Sulfadiamine OR DADDS OR Diacetyldapsone OR 4',4'''-Sulfonylbis(acetanilide) OR Acetyldiphenazonum OR Rodilone OR Hansolar OR *Mycobacterium bovis* or BCG or Calmette-Guerin Bacillus OR BCG Vaccine OR Bacillus Calmette Guerin Vaccine OR Calmette Guerin Bacillus Vaccine OR Calmette's Vaccine OR Calmette Vaccine OR Calmettes Vaccine OR BGC immunotherapy OR BCG vaccination) AND (Leprosy OR Leprosies OR Hansen Disease OR Hansen's Disease OR Hansens Disease)

adequacy of sequence generation; allocation sequence concealment; blinding of participants and caregivers; blinding of data collectors; blinding for outcome assessment; blinding of data analysts; incomplete outcome data; selective outcome reporting; and the presence of other potential sources of bias not accounted for in other domains (Guyatt and Busse 2017). For incomplete outcome data, we stipulated loss to follow-up rates of less than 20% as being low risk of bias. Conflicts were resolved via discussion, with third party adjudication as necessary.

Certainty of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to rate certainty of the evidence for each outcome as high, moderate, low, or very low (Guyatt et al 2008). Detailed GRADE guidance was used to assess overall risk of bias (Guyatt et al 2011a), imprecision (Guyatt et al 2011b), inconsistency (Guyatt et al 2011c), indirectness (Guyatt et al 2011d) and publication bias (Guyatt et al 2011e), with results summarized in an evidence profile. Publication bias was assessed through visual inspection of funnel plots for outcomes with 10 or more studies.

Data synthesis and statistical analysis

We analyzed all outcomes as dichotomous variables. We calculated risk ratios (RRs) with 95% confidence intervals (CIs). The unit of analysis was each participant recruited into the trials. We used Cochrane's statistical software Review Manager 2014 for data analysis (Nordic 2011). Random-effect models were used to analyze data (with two or more studies), and number needed to treat (NNT) was calculated for statistically significant results.

To deal with missing data, we used complete case analysis as our primary analysis; that is, we excluded participants with missing data. One exception to this was made for the Wardekar 1969 study, which did not provide data related to drop-outs or participants lost to follow-up; here, we used the number of randomized patients as the denominator.

Where results of the primary analysis achieved or approached statistical significance, we conducted sensitivity analyses to test the robustness of those results. Specifically, we conducted a plausible worst-case sensitivity analysis in which all participants with missing data were assumed to also have leprosy (Akl et al 2015, Akl et al 2013). In cases of substantial heterogeneity (I2> 50%), we investigated potential causes of heterogeneity and, where data permitted, planned to carry out subgroup analyses based on: chemoprophylaxis regimens (e.g., rifampicin versus dapsone); control groups (e.g., placebo versus BCG alone); and types of contacts (e.g., household and social).

When authors provided data for different time points, we presented the data for the longest follow-up related to the time period of the meta-analysis.

Results

Selection of titles : Of 535 unique hits identified by the electronic search and additional articles from reference list searching and content expert suggestion, 82 titles and abstracts were deemed potentially eligible. Six studies, including two cluster RCTs involving 48,096 participants and four parallel RCTs involving 4,387 participants, were finally deemed eligible for inclusion (Feenstra et al 2012, Wardekar 1969, Neelan et al 1986, Noordeen and Neelan 1978, Noordeen and Neelan 1976, Dharmendra et al 1965) (Fig 1; Appendix Table 2).

Study Characteristics : All included studies were conducted in Asia: five studies were based in India (Wardekar 1969, Neelan et al 1986, Noordeen and Neelan 1978, Noordeen and Neelan 1976,

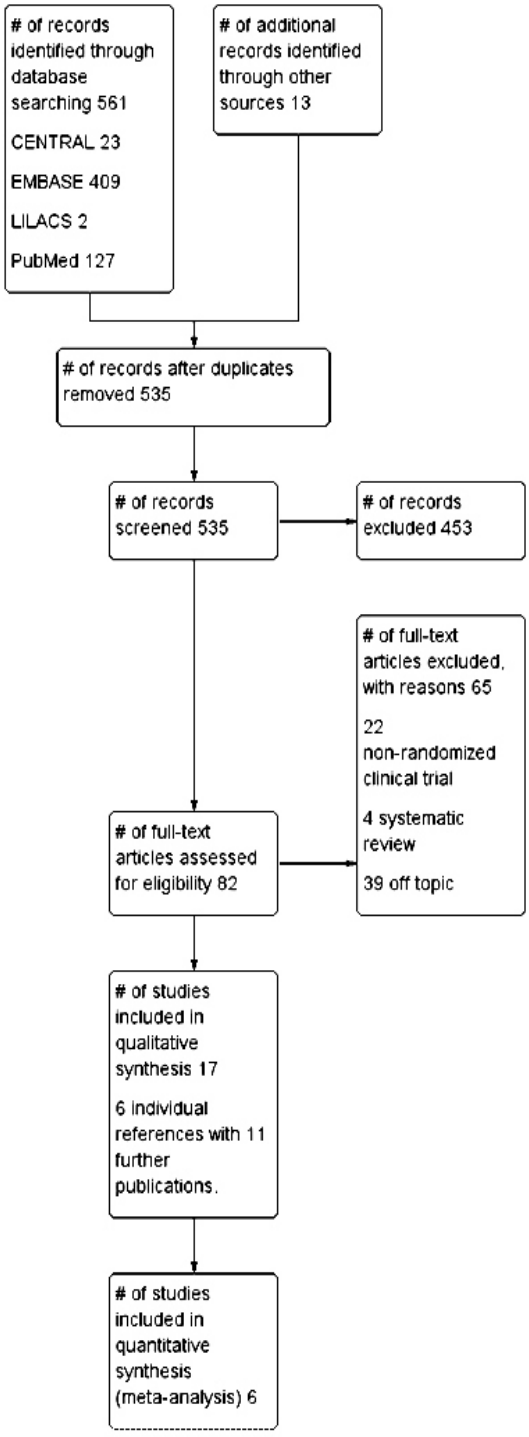

Fig 1 : Flow chart of the review.

Dharmendra et al 1965) and one in Bangladesh (Feenstra et al 2012). Randomized trials sample size ranged from 700 (Dharmendra et al 1965) to 26,385 participants (Wardekar 1969). Only one study reported the mean age of participants, indicating they were close to 30 years of age (Feenstra et al 2012). Studies followed participants from two years to six years (Table 1).

All included studies used placebo as the control group. Four RCTs used dapsone (Wardekar 1969, Noordeen and Neelan 1978, Noordeen and Neelan 1976, Dharmendra et al 1965), one RCT used acedapsone (Neelan et al 1986), and RCT trial used rifampicin (Feenstra et al 2012) (Table 2).

Risk of Bias Assessment : The major issue regarding risk of bias across the included RCTs was the of selective outcome reporting (Feenstra et al 2012, Wardekar 1969, Noorden and Neelan 1978, Noordeen and Neelan 1976, Dharmendra 1965). Additionally, four studies were rated as high risk of bias for limitations in blinding of data collectors (Feenstra et al 2012, Wardekar 1969, Neelan et al 1986, Noorden and Neelan 1978), and three studies were rated as such for limitations in allocation concealment (Wardekar 1969, Noorden and Neelan 1978, Dharmendra 1965) (Fig. 1).

Outcomes

Meta-analysis of clinical leprosy in contacts up to two years follow-up : Pooled results from two RCTs (Feenstra et al 2012, Wardekar 1969) with a total of 45,029 participants showed a significant reduction in clinical leprosy in contacts up to two years with chemoprophylaxis compared to placebo (RR 0.32, 95% CI 0.17, 0.62; $p < 0.0007$; I^2=70%, p=0.07; NNT = 256) (Figure 3a). Certainty in evidence was rated down to low because of risk of bias and inconsistency, missing outcome data, lack of blinding of participants, caregivers, data collectors, statistician, and outcome assessors

Table 1 : Study characteristics related to design of study, setting, number of participants, mean age, gender, and follow-up.

Author, year	Design of RCT	Country Setting	Number of randomize participants	Mean age per studied group	Gender (male %)	Follow -up (years)
Feenstra 2012 [9]	RCT cluster	Bangladesh Districts Rangpur and Nilphamari. India	21,711 I: 10,857 P: 10,854	I: 31.5€ P: 29.9€	I: 23.1 P: 23	6
Neelan 1986 [27]	Parallel RCT	Madras city (Tamil Nadu state). India	700 I: 350 P: 350	NR	52,5	4.7
Noordeen 1978 [28]	Parallel RCT	Sriperumbudur Taluk Chengalpattu district (Tamil Nadu state). India	955 I: 636 P: 319	NR	NR	6
Noordeen 1976 [29]	Parallel RCT	Chingleput district. (Tamil Nadu state). India	2,000 I: 1,000 P: 1,000	NR	NR	3.5
Wardekar 1969 [42]	RCT cluster	Small area near Chilakalapalli, about 14 miles from Bobbili (Andhra Pradesh state). India	26,385* I: 13,061* P: 13,324*	NR	NR	4.5
Dharmenda 1965 [8]	Parallel RCT	Chingleput district (Tamil Nadu state). India	732 I: 368 P: 364	NR	55	2.3

I: intervention group; P: placebo; NR: not reported; € The mean age was based on the mean age from each group reported in the Feenstra 2012 study [9].

*From 54 villages.

(Wardekar 1969), lack of selective outcome reporting (Feenstra et al 2012, Wardekar 1969) (Figs. 2 and 3a, Table 3).

Meta-analysis of clinical leprosy in contacts two to five years follow-up, inclusive : Pooled results from five RCTs (Feenstra et al 2012, Wardekar 1969, Neelan et al 1986, Noorden and Neelan 1976, Dharmendra 1965) with a total of 47,989 participants showed a significant reduction in clinical leprosy in contacts from two years to five years with the use of chemoprophylaxis compared to placebo (RR 0.51, 95% CI 0.29, 0.89; p=0.02; I^2=80%, p<0.0005; NNT = 256) (Fig. 3a). Certainty in evidence was rated down to low because of risk of bias and inconsistency, missing outcome data (Wardekar 1969, Dharmendra 1965), lack of selective outcome reporting (Feenstra et al 2012, Wardekar 1969, Noorden and Neelan 1976, Dharmendra 1965) and lack of blinding of participants, caregivers (Feenstra

Table 2 : Study Characteristics related to description of intervention and control groups, and outcomes

Author, year	Description of intervention	Description of control	Measured outcomes
Feenstra 2012 [9]	Single dose rifampicin 600 mg for adults weighing 35 kg and over, 450 mg for adults weighing < 35 kg and for children > 9 years, and 300mg for children aged 5-9 years. Time: 1 day.€	Placebo.	Development of clinical leprosy.
Neelan 1986 [27]	Acedapsone 225mg intramuscularly once every 10 weeks for children of 6 to 15 years of age, and 150mg for children of 1 to 5 years of age. Time: 3 years	Placebo injection	Development of clinical leprosy.
Noordeen 1978 [28]	Dapsone (age 1-2 years, 10mg or 5mg; 3-5 years, 25mg or 10mg; 6-10, 50mg or 25mg; > 11 years, 75mg or 50mg) once a week. Time: NR	Placebo tablets of Di-calcium phosphate once a week	Development of clinical leprosy.
Noordeen 1976 [29]	Dapsone (age 0-2 years, 10mg; 3-5 years, 25mg; age 5-10 years, 50 mg; over 11 years of age, 75mg) twice a week. Time: over 1 or 2 years	Placebo tablets of Di-Calcium phosphate	Development of clinical leprosy.
Wardekar 1969 [42]	Dapsone (age 0-2 years, 5 a 20mg; 3-5 years, 10 a 40 mg; 6-10 years, 25 a 100mg; 11-15 years, 50 a 150mg; 16-25 years, 50 a 300 mg) every 2 weeks. Time: 4 ½ years	Placebo.	Development of clinical leprosy.
Dharmendra 1965 [8]	Dapsone (age 0-2 years, 10 mg; 3-5 years, 20 mg; age 6-10 years, 50 mg; over 11 years of age, 75mg) twice a week. Time: over 3 years	Placebo tablets of di-calcium phosphate	Development of clinical leprosy.

Mg: milligrams; Kg: Kilogram, NR: not reported.

€ The authors retrospectively reviewed whether the participants had received BCG in the past, and they also analyzed it separately in four groups.

et al 2012, Wardekar 1969), data collectors, statistician, and outcome assessors (Feenstra et al 2012, Wardekar 1969, Neelan et al 1986) (Figs. 2 and 3a, Table 3).

Meta-analysis and sensitivity analysis of clinical leprosy in contacts two years to five years follow-up, inclusive, excluding Feenstra 2012 and Wardekar 1969 : Sensitivity analysis excluding both Feenstra (2012) and Wardekar (1969) studies yielded results that were consistent with the primary analysis (RR 0.59, 95% CI 0.47, 0.75; p < 0.0001; I^2=0%, p=0.39; NNT = 21) (Fig. 3b). The

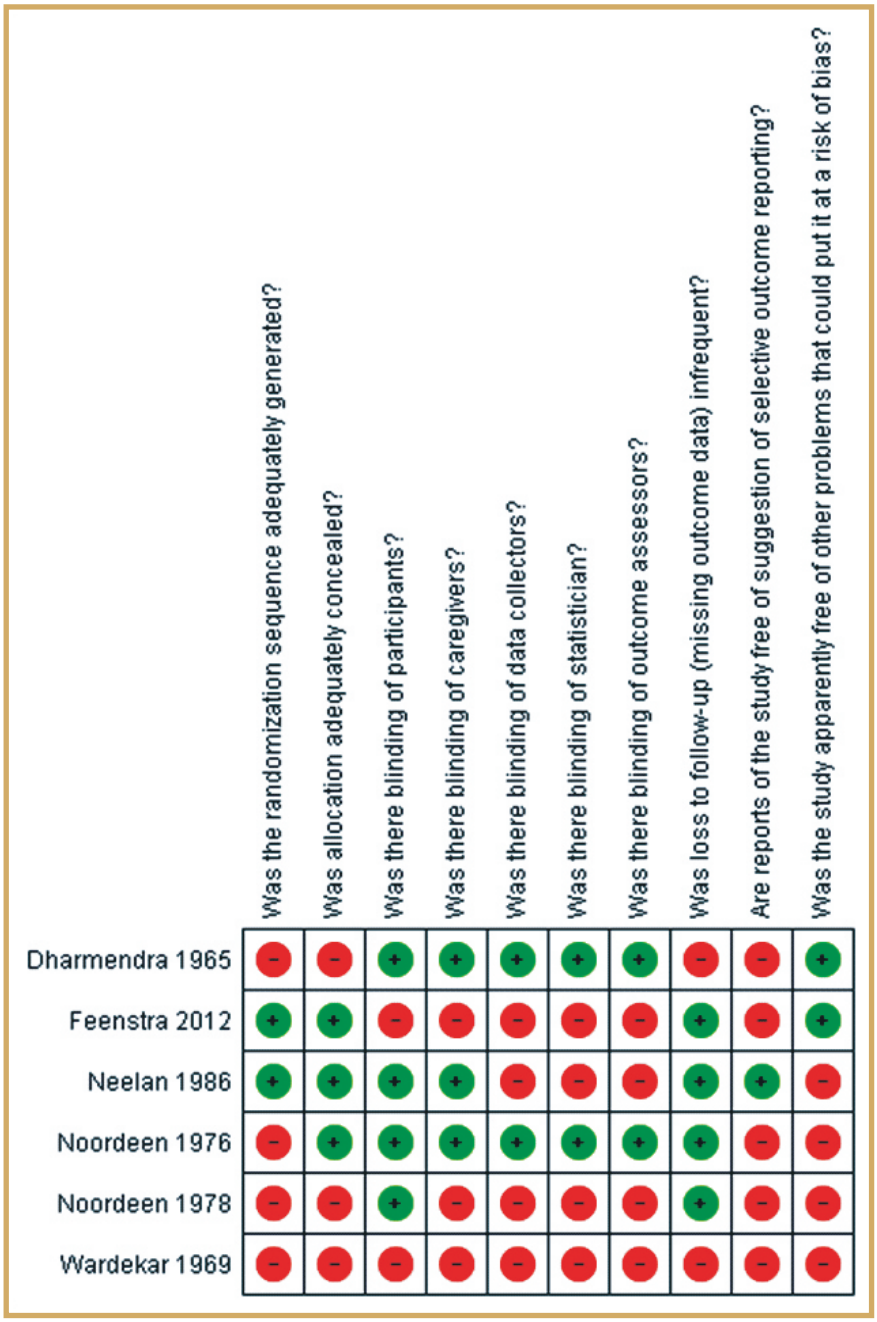

Fig. 2 : Risk of bias assessment.

*After four years the Feenstra 2012 study was unblinded.

All responses as likely were not coupled as definitely not, and are represented by the balls in red or with sina (-) as a high risk of bias, and all responses were probably coupled with the definite category yes, which indicates that the study has a low bias index symbolized by green polka dots or a (+) sign.

Appendix Table 2 : Information about multiple publications of the same study

Author, year	References of multiple publications	Reasons on whether to include or not these publications
Feenstra 2012 [9]	Feenstra SG, Pahan D, Moet FJ, Oskam L, Richardus JH. Patient-related factors predicting the effectiveness of rifampicin chemoprophylaxis in contacts: 6 year follow up of the COLEP cohort in Bangladesh. Leprosy review. 2012; 83(3):292-304. Schuring RP, Richardus JH, Pahan D, Oskam L. Protective effect of the combination BCG vaccination and rifampicin prophylaxis in leprosy prevention. Vaccine. 2009; 27(50): 7125-7128. Moet FJ, Pahan D, Oskam L, Richardus JH; COLEP Study Group. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. British medical journal. 2008; 336(7647): 761-764.	They are all part of COLEP study. We considered Feentra 2012 study as the main publication because it presented outcomes from the longest follow-up.
Neelan 1986 [27]	Neelan PN, Sirumban P, Sivaprasad N. Limited duration acedapsone prophylaxis in leprosy. Indian journal of leprosy. 1986; 58(2): 251-256. Neelan PN, Noordeen SK, Sivaprasad N. Chemoprophylaxis against leprosy with acedapsone. Indian J Med Res. 1983 Sep; 78: 307-13. Noordeen SK, Neelan PN, Munaf A. Chemoprophylaxis against leprosy with acedapsone. An interim report. Leprosy in India. 1980; 52(1): 97-103.	We considered the main study Neelan 1986 because presented outcomes from the longest follow-up.
Noordeen 1976 [29]	Noordeen SK, Neelan PN. Extended studies on chemoprophilaxis against leprosy. Indian journal of medical research. 1978; 67: 515-527. Noordeen SK, Neelan PN. Chemoprofilaxis among contacts of lepromatous leprosy. Leprosy in India. 1976; 48(4): 635-642.	We considered both publications as different studies because although Noordeen 1978 study included data from 1976, they also presented data from another trial.
Wardekar 1969 [42]	Wardekar RV. Chemoprophilaxis in Leprosy. Leprosy in India. 1969; 241-246. Wardekar RV. DDS prophylaxis against leprosy. Leprosy in India. 1967; 39: 155-159.	We considered Wardekar 1969 study as the main publication because it presented outcomes from the longest follow-up.

Darmendra 1965 [8]	Noordeen SK. Long term effects of Chemoprophilaxis among contacts of Lepramatous cases-results of a 8.5 follow up. Leprosy in India. 1977; 49(4): 504-509. Noordeen SK. Chemoprophilaxis in Leprosy. Leprosy in India. 1969; 41: 247-254. Noordeen SK. Chemoprophylaxis in Leprosy. Leprosy in India. 1968: 115-119. Dharmendra, Noordeen SK, Ramanujam K. Prophylactic value of DDS against leprosy - a further report. Leprosy in India. 1967; 39: 100-106. [No authors listed]. Chemoprophylaxis in leprosy. British Medical Journal. 1966; 21: 1(5498): 1252. Dharmendra, Ali PM, Noordeen SK and Ramanujam K. Prophylactic Value of DDS against leprosy-na interium report - Leprosy in India. 1965; 37: 447-467.	We considered Darmendra 1965 study as the main publication because it presented the most complete and largest data: although we used the other publications to verify further data.

reason for exclusion was due to the length of time the drug was used.

Meta-analysis of clinical leprosy in contacts two years to five years follow-up (worst-case sensitivity analysis, excluding Feenstra 2012 and Wardekar 1969 : Pooled results from three RCTs (Neelan et al 1986, Noorden and Neelan 1976, Dharmendra et al 1965) with a total of 3,432 participants showed a significant reduction in clinical leprosy in contacts from two years to five years with chemoprophylaxis compared to placebo (RR 0.88, 95% CI 0.79, 0.98; p=0.02; I^2=0%, p<0.69 NNT = 33) (Fig. 3b). Certainty in evidence was rated down to moderade because of risk of bias, missing outcome data (Neelan et al 1986, Dharmendra et al 1965) lack of selective outcome reporting (Noorden and Neelan 1976, Dharmendra et al 1965) and lack of blinding of data collectors, statistician and outcome assessors (Neelan et al 1986) (Figs. 2 and 3b, Table 3).

Meta-analysis of clinical leprosy in contacts > five years follow-up : Pooled results from two RCTs (Feenstra et al 2012, Noorden and Neelan 1978) with a total of 18,480 participants did not show a significant reduction in clinical leprosy in contacts over five years with chemoprophylaxis compared to placebo (RR 0.77, 95% CI 0.46, 1.28; p =0.31; I^2=48%, p=0.16) (Figure 3a). Certainty in evidence was rated down to low because of imprecision and risk of bias, lack of selective outcome reporting and lack of blinding of caregivers, data collectors, statistician (Feenstra et al 2012, Noorden and Neelan 1978), outcome assessors and participants (Feenstra et al 2012) (Figs. 2 and 3a, Table 3).

Meta-analysis of clinical leprosy in contacts with only dapsone, regardless of the follow-up periods : Pooled results from three RCTs (Noorden and Neelan 1978, Noorden and Neelan 1976, Dharmendra et al 1965) with a total of 3,102 participants showed a significant reduction in clinical leprosy in contacts with only dapsone, regardless of follow-up duration, compared to placebo (RR 0.63, 95% CI 0.51, 0.78; p < 0.0001;

Table 3 : GRADE evidence profile: chemophophylaxis to prevent clinical leprosy in contacts

No of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Study event rates Placebo* Intervention	Relative risk (95% CI)	Anticipated absolute effects over 6-12 months Placebo* Intervention	OR certainty of evidence
Clinical leprosy in contacts up to 2 years									
45,029 (2)[9,42]	Serious limitations[1]	Serious limitations[2]	No serious limitations	No serious limitations	Undetected	P: 132/22,730 I: 43/22,299	**0.32** (0.17-0.62)	P: 7 per 1000 I: 5 fewer per 1000 (6 fewer to 3 fewer)	LOW
Clinical leprosy in contacts from 2 to 5 years									
47,989 (5)[8,9,27,29,42]	Serious limitations[1]	Serious limitations[2]	No serious limitations	No serious limitations	Undetected	P: 228/24,126 I:132/23,863	**0.51** (0.29-0.89)	P: 129 per 1000 I:64 fewer per 1000 (92 fewer to 14 fewer)	LOW
Clinical leprosy in contacts from 2 to 5 years (worst-case sensitivity analysis)									
3,432 (3)[8,27,29]	Serious limitations[1]	Serious limitations	No serious limitations	No serious limitations	Undetected	P: 495/1,714 I: 435/1,718	**0.88** (0.79-0.98)	P: 266 per 1000 I: 234 fewer per 1000 (54 fewer to 5 fewer)	MODE-RADE
Clinical leprosy in contacts over 5 years									
18,480 (2)[9,28]	Serious limitations[1]	Serious limitations	No serious limitations	No serious limitations[3]	Undetected	P: 55/9,147 I: 71/9,333	**0.77** (0.46-1.28)	P: 148 per 1000 I: 34 fewer per 1000 (80 fewer to 41 more)	LOW
Adverse effects									
Outcome not reported						Outcome not reported	Not estimable	Not estimable	VERY LOW

I: intervention; P: placebo; Number of studies indicated within parenthesis; superscript study reference in the list of references

*The estimated risk control was taken from the study that presented higher weight in the meta-analysis.

[1] There were serious limitations related to blinding [Feenstra 2012; Neelan 1986; Noordeen 1978; Wardekar 1969], generation [Dharmendra 1965; Noordeen 1978; Noordeen 1976; Wardekar 1969] and allocation concealment [Dharmendra 1965; Noordeen 1978; Wardekar 1969], and related to missing outcome data in all studies [Dharmendra 1965; Wardekar 1969].

[2] I^2 > 50% with a p value > 0.10.

[3] 95% CI for absolute effects include clinically important benefit and no benefit.

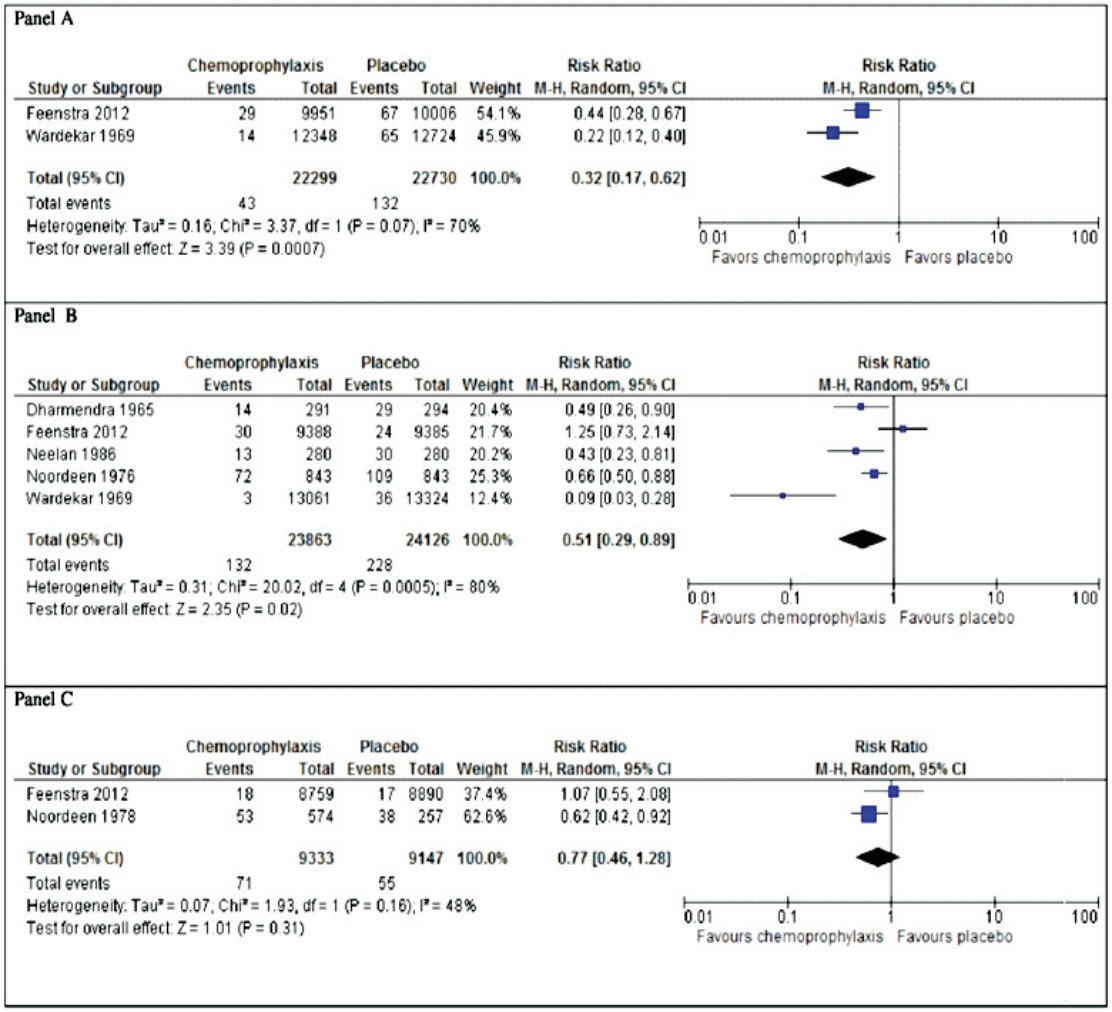

Fig. 3a : Meta-analysis of clinical leprosy in contacts.

(Panel A: Meta-analysis of clinical leprosy in contacts up to two years follow-up. Panel B: Meta-analysis of clinical leprosy in contacts two years to five years follow-up, inclusive. Panel C: Meta-analysis of clinical leprosy in contacts > five years follow-up.)

I^2=0%, p=0.68 NNT = 22) (Fig. 3b). Certainty in evidence was rated down to moderate because of risk of bias, missing outcome data (Dharmendra et al 1965), lack of selective outcome reporting (Noorden and Neelan 1978, Noorden and Neelan 1976, Dharmendra et al 1965) and lack of blinding of caregivers, data collectors, statistician and outcome assessors (Noorden and Neelan 1978) (Fig. 2 and 3b).

Only Neelan et al (1986) reported on adverse events, however no patients experienced it.

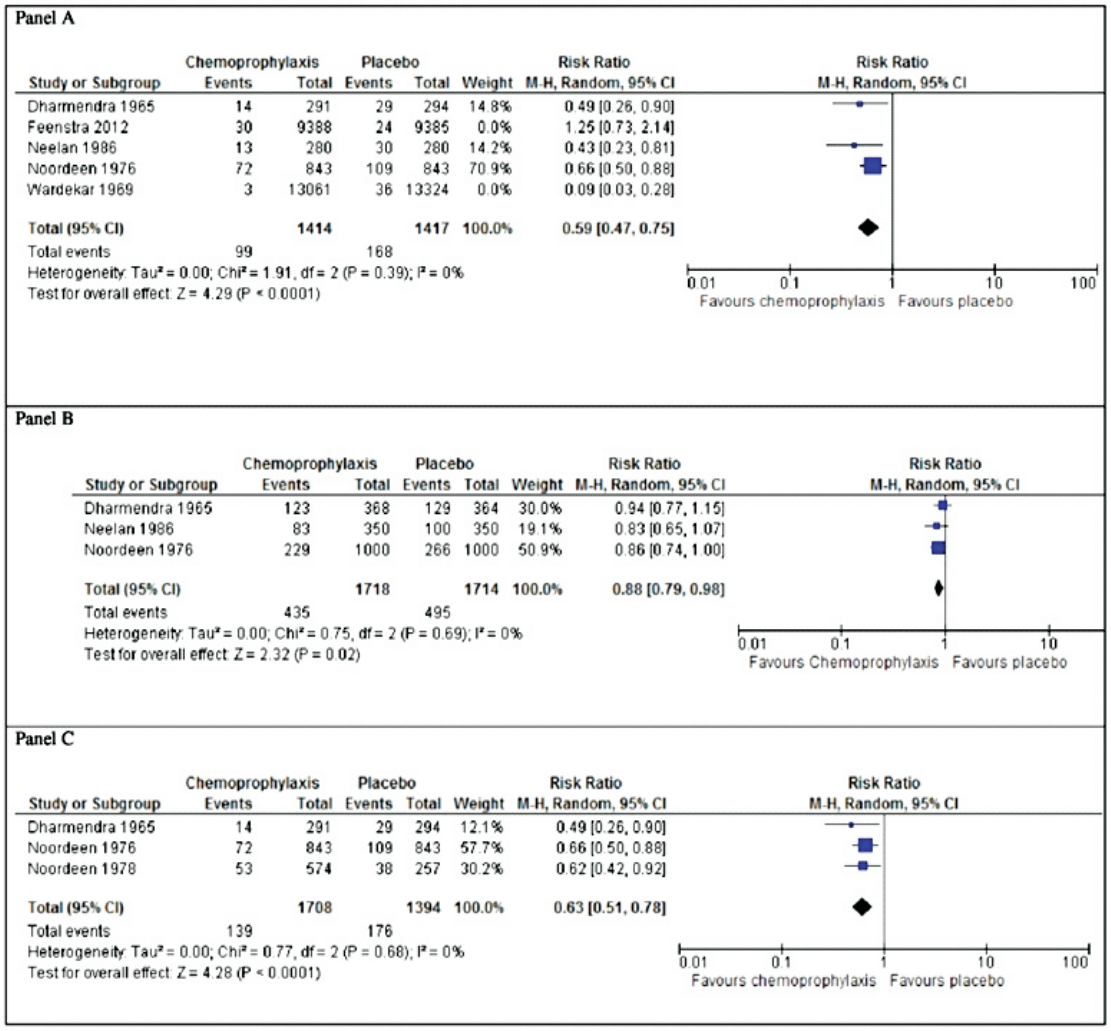

Fig. 3b : Sensitivity analysis of clinical leprosy in contacts.

(Panel A sensitivity analysis of clinical leprosy in contacts two years to five years follow-up, inclusive, excluding Feenstra 2012 and Wardekar 1969. Panel B meta-analysis of clinical leprosy in contacts two years to five years follow-up (worst-case sensitivity analysis, excluding Feenstra 2012 and Wardekar 1969). Panel C meta-analysis of clinical leprosy in contacts with only dapsone, regardless of the follow-up periods.)

Discussion

Leprosy is no longer a public health problem in developed countries; elimination in these settings has been made possible by tremendous scientific, social and economic developments combined with necessary access to care (Pedrazzani et al 1998, Nsagha et al 2011). However, the number of new cases in endemic countries remains high, and continues to rise/ remain stagnant in continents such as Africa

and Asia. Leprosy also affects the pediatric population. Delayed or missed diagnoses of contagious index cases and inadequate adherence to treatment are likely significant contributors to transmission of disease and high / stagnant new case load (WHO 2017).

The results of this review suggest that transmission rates among contacts of leprosy patients may be reduced with the PEP use of chemoprophylaxis, with no clear evidence to this effect with five years of follow-up. Over five years, no significant difference was found between chemoprophylaxis compared to placebo. Contacts are considered under high risk until the fifth year of identification of the index case, with close surveillance and management of contacts in the interim recommended by numerous authorities internationally (Ministério da Saúde 2016).

While two studies (Feenstra et al 2012, Wardekar 1969) were excluded in the sensitivity analysis and were found to introduce significant heterogeneity into the meta-analysis, the results of the analysis were consistent with the primary analysis. Interestingly, both studies showed significant differences favoring chemoprophylaxis, with the former study presenting statistically significant results with a single dose rifampicin, though only up to two years. This strategy is in contrast to older studies, which involved chemoprophylaxis regimens with significantly increased frequencies and longer durations of use (Wardekar 1969, Neelan et al 1986, Noordeen and Neelan 1976, Dharmendra et al 1965). While potentially more effective, longer and more frequent prophylactic regimens may be of low viability due to the significant cost of medications and concerns regarding development of drug resistance.

Relation to prior work

The results of our review are consistent with the findings of previous reviews (Smith and Smith 2000, Bhalla 2015, Reveiz et al 2009) which suggest that chemoprophylaxis is effective for the prevention of leprosy among contacts; however, our review attempted to avoid overlapping of patients in the meta-analysis, and was the only review that included the results of 6-years follow-up from the study with 17,649 participants (Feenstra et al 2012). A recent review presented only partial data from participants in the intervention arms of the Nordeen 1978 RCT, which has been fully presented here (Reveiz et al 2009).

Recent literature recommends the Leprosy Post-Exposure Prophylaxis (LPEP) strategy with single-dose Rifampicin (SDR) as a blanket approach to chemoprophylaxis for leprosy contacts (Smith et al 2017, Barth-Jaeggi et al 2016). The regimen is estimated to reduce infectivity by 50-60% within two years of administration and is an alternative measure in the absence of reliable tools to diagnose infection (Steinmann et al 2017). Feenstra et al (2012) have shown that single-dose rifampicin is effective for disease prevention. The regimen is particularly effective in combination with the BCG vaccine (Shuring et al 2009). Oo KN et al (2008) have similarly advocated for single-dose rifampicin, but have recommended combination with ofloxacin and minocycline for appropriate prophylaxis.

Studies evaluating feasibility and effectiveness of single-dose rifampicin for leprosy chemoprophylaxis are underway, including the Leprosy Post-Exposure Prophylaxis (LPEP) study, which began in 2015 and is expected to be completed by 2018. The study involves numerous endemic regions, including India, Indonesia, Myanmar, Nepal, Sri Lanka and Tanzania. The PEP-Hans study, based in Brazil, represents a similar ongoing effort in municipalities like Mato Grosso, Pernambuco and Tocantins (Barth-Jaeggi et al 2016). A Cambodian retrospective cohort study (Fürst et al 2018) and MALTALEP study are similar

in nature, the latter evaluating whether the BCG vaccine plus rifampicin are effective in combination for prophylaxis (Richardus et al 2013).

Discourse regarding drug resistance concerns has been varied. There is some suggestion that rifampicin poses a negligible risk of generating resistance in *M. tuberculosis* at the population level, and as such, that benefits of reduced leprosy risk significantly outweigh drug resistance risks for tuberculosis. Risk factor for inducing drug resistance in *M. leprae* are still unknown, therefore, regular sampling and molecular monitoring of mutations associated with resistance to Rifampicin have been recommended to be performed in areas where SDR is actively used (Mieras et al 2016).

Evidence supports tools such as anti-phenolic glycolipid I (PGL1) serology, Mitsuda test, and the BCG vaccination in combination as part of an active disease control program to reduce disease severity and protect household contacts in particular (Araujo et al 2015). While the vast majority of contacts do not develop clinical leprosy, monitoring of contacts once yearly at minimum is important, given findings suggesting that new cases are typically detected within the first year of monitoring (Araujo et al 2015, Jarbuli et al 2014, Gomes et al 2015).

This meta-analysis has shown that there is an urgent need for more evidence regarding whether leprosy chemoprophylaxis is effective either with single or combination prophylactic regimens. While existing evidence includes numerous large-scale RCTs, special attention is warranted towards future RCTs with intention-to-treat analyses, adequate randomization and appropriate blinding.

It should be noted that while only one study reported post-intervention adverse events, no such events were reported, suggesting that chemoprophylactic regimens were generally d well-tolerated and safe (Neelan et al 1986). Given the limited evidence, for these outcomes more studies are needed to assess the safety of chemoprophylactic regimens in use.

There is no consensus in the literature about thresholds for NNT (numbers needed to treat) for leprosy. Here, we considered NNT < 25 of great relevance, NNT 25-50 of moderate relevance and 50-100 of small relevance (Correia 2012). This was based on the fact that leprosy is largely a non-acute non-fatal condition, the bacilli shows low pathogenicity and low virulence affecting a relatively small proportion of the population, and typically involves long-term interventions. This may have statistically justified a NNT of 256 in the primary analysis up to two years and from two to five years follow-up. It is important to consider that NNT may decrease when it reaches a larger part of the population in an indirect way. In addition to that, the sensitivity analysis revealed an NNT of 21, showing the great benefits of chemoprophylaxis.

Strengths and Limitations

Strengths of our review include: conduct of a comprehensive search; assessment of eligibility, risk of bias and data abstraction independently and in duplicate; assessment of risk of bias; conduct the sensitivity analysis addressing loss to follow-up; and use of the GRADE approach in rating the certainty of evidence for each outcome.

The primary limitation of our review was the substantial loss to follow-up. Insufficient data on adverse events precluded statistical analysis for safety outcomes. Publication bias was not assessable as well, given less than 10 studies were identified for any given outcome. Subgroup analyses were planned for different chemoprophylaxis regimens, control groups, and contact types, but were not conducted except for a subgroup analysis for dapsone, as less than two studies were available for all other such analyses.

Finally, randomization and allocation concealment were unclear due to reporting limitations, and most studies were classified as high risk of bias with blinding of outcome assessors being a significant concern. The findings of our review should be considered in light of these limitations.

Another limitation of our review is the fact that with exeption of Feenstra et al (2012) study, the remaining included studies in this review were conducted in the 1960s to 1980s which the prevalence were more than 5 million cases differing hugely from nowadays' data. However, the current reduction of more than 200,000 cases in 2016 (WHO 2017) were found only in developed countries, and the scenario still remains a public health issue in developing countries such as Banglasdesh, India, and Brazil justifying the study of chemoprophylaxis and other treatments.

Implications : The World Health Organization 2016-2020 global strategy recommends reductions in the incidence of leprosy and degree of disability, as well as steps towards eradication of the disease in children (WHO 2016). Given its high transmissibility and social, economic, health and quality of life burdens, eradication of leprosy and reduction in its transmission represent fundamental public health challenges internationally.

Low-certainty evidence shows that chemoprophylaxis is effective in the reduction of clinical leprosy in contacts up to two years and lesser efficacy was observed in two to five years follow-up. However, low-certainty evidence shows that there is no significant effect of chemoprophylaxis over five years. No conclusions can be drawn concerning adverse events.

Further well-designed studies are warranted to better support recommendations for routine implementation of chemoprophylaxis, particularly with focuses on long-term efficacy, safety, acceptability and quality of life, feasibility and cost-effectiveness, and drug resistance rates. Comparison of therapeutic regimens is also limited and is necessary to guide recommendations of appropriate chemoprophylaxis for moving forward.

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How to cite this article : Ferreira APM, Fan W, Agarwal A et al (2018). Chemoprophylaxis for Contacts of Leprosy Patients: A Systematic Review and Meta-analysis. *Indian J Lepr.* **90** : 217-234.