UNIVERSIDADE ESTADUAL PAULISTA
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ANA PAULA DO PRADO MARQUES FERREIRA

Quimioprofilaxia para os contatos de pacientes com hanseníase: uma revisão sistemática e metanálise.

Dissertação apresentada à Faculdade de Medicina da Universidade Estadual Paulista "Júlio de Mesquita Filho", Campus de Botucatu, para obter o título de Mestra em Bases Gerais de Cirurgia.

Orientadora: Dra. Regina Paolucci El Dib
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Palavras-chave: GRADE; Hanseníase; Prevenção; Quimioprevenção; Revisão sistemática; Metanálise.

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RESUMO

Introdução: Indivíduos que estão em estreita associação ou proximidade com pacientes com hanseníase têm maior chance de adquirir a doença. A eficácia da quimioprofilaxia na prevenção da hanseníase nos contatos dos pacientes afetados para um ótimo controle da doença ainda não é clara. **Métodos**: pesquisas eletrônicas de Medline, EMBASE, CENTRAL e LILACS até outubro de 2017 foram realizadas para identificar estudos elegíveis. As listas de referência de estudos potencialmente elegíveis foram revisadas. Incluímos ensaios clínicos randomizados (RCTs) que compararam a quimioprofilaxia com placebo para a prevenção da infecção da hanseníase em contatos de pacientes afetados. O par de revisores examinou de forma independente artigos elegíveis, extraiu dados e avaliou o risco de viés. A abordagem GRADE foi utilizada para avaliar a certeza geral da evidência. **Resultados**: seis ECRs, incluindo 52.483 participantes, se mostraram elegíveis. Os resultados sugeriram uma redução estatisticamente significativa na hanseníase clínica em contatos até dois anos (Rácio de Risco (RR) 0,32, Intervalo Confidencial (IC) 0,11 0,62; p <0,0007; I2 = 70%, p = 0,07; evidência de qualidade) e de dois a cinco anos de seguimento (RR 0,51, IC 95% 0,29, 0,89; p = 0,02; I2 = 80%, p <0,0005; evidência de baixa qualidade) com o uso de

quimioprofilaxia em comparação com placebo. No entanto, os resultados sugeriram uma redução não significativa na hanseníase clínica nos contatos ao longo de cinco anos (RR 0,77, IC 95% 0,46, 1,28; p = 0,31; I2 = 48%, p = 0,16; evidência de baixa qualidade).

Conclusões: evidências de baixa qualidade mostram que a quimioprofilaxia é efetiva na redução da hanseníase clínica em contatos até dois anos e de dois a cinco anos. No entanto, evidências de baixa qualidade mostram que não há efeito significativo da quimioprofilaxia ao longo de cinco anos.

Palavras-chave: quimioprofilaxia; hanseníase; prevenção; GRAU; revisão sistemática; meta-análise.

SUMMARY

ARTICLE

Chemoprophylaxis for contacts of leprosy patients: a systematic review and meta-analysis

Running title: Chemoprophylaxis for contacts of leprosy patients

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CONFLICTS OF INTEREST

The authors report no conflicts of interest. The funding agency played no role in the conduction of the research or preparation of the manuscript.

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ABSTRACT

Background: Individuals who are in close association or proximity with leprosy patients have a greater chance of acquiring the disease. The effectiveness of chemoprophylaxis in preventing leprosy in contacts of affected patients for optimal disease control remains unclear.

Methods: 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. 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.

Results: 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-quality 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-quality 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-quality evidence).

Conclusions: Low-quality 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, low-quality evidence shows that there is no significant effect of chemoprophylaxis over five years.

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

BACKGROUND

Leprosy, also known as Hansen's disease, is an infectious chronic disease caused by *Mycobacterium leprae*[1], 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[2,3,4].

More than three million persons are disabled by leprosy worldwide[5]. Disease burden is greatest in developing countries like India, Brazil, the Democratic Republic of Congo, Tanzania, Nepal, Madagascar and Mozambique[3,6]. In 2016, 12,819 of new cases had grade 2 disabilities (i.e., loss of protective sensation and visible deformities), an increase compared to previous years. In Brazil, the number of cases classified as grade 2 in 2016 was 1,736[7].

Transmission of leprosy possibly occurs through nasal secretions or droplet contact of an infected person[1]. As such, 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[8]. In the absence of an effective vaccine, disease prevention relies largely on 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[9, 10]. Multi-drug chemotherapy with rifampicin, dapsone and clofazimine (multidrug treatment) is the primary therapeutic strategy for leprosy[10].

To prevent leprosy transmission, some studies suggest that chemoprophylaxis combined with the receipt of the Bacillus Calmette–Guérin (BCG) vaccine may be a promising strategy for the future control of leprosy[3, 11].

Two previous systematic reviews have been conducted examining chemoprophylaxis for leprosy prevention[12,13]. 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[12,13]. A more recent systematic review[14] evaluating chemoprophylaxis for leprosy prevention among contacts of newly-diagnosed patients has been published, but failed to include a landmark RCT with 21,711 participants[15]. 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[16].

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[17].

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).

(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)

Appendix Table 1. Search strategy.

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[18] (http:/distillercer.com/resources/)[19] that included nine domains: 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[19]. 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[20]. Detailed GRADE guidance

was used to assess overall risk of bias[21], imprecision[22], inconsistency[23], indirectness[24] and publication bias[25], 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[26] for data analysis. 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[27], 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[28,29]. In cases of substantial heterogeneity ($I^2 > 50\%$), 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[15,27,30-33] (Figure 1; Appendix Table 2).

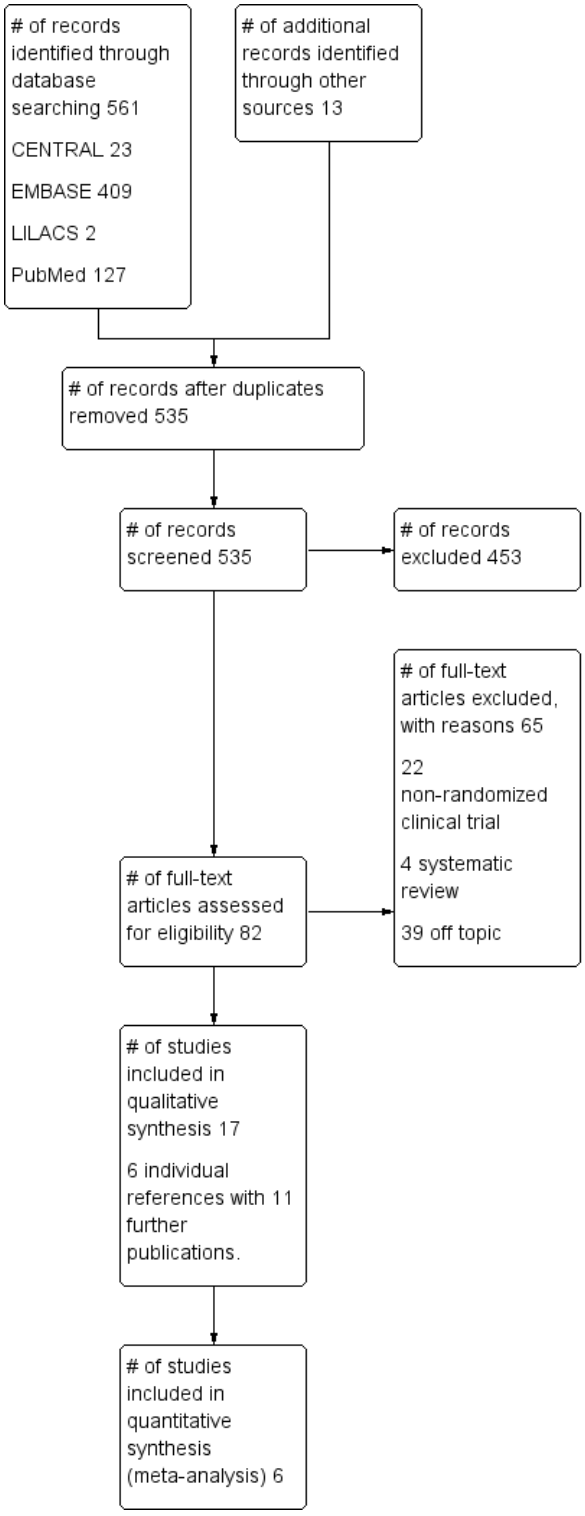


Figure 1. Flowchart of the review.

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 [15]	- 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 [29]	- 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 [31]	- 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 [25]	- 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 [32]	**- 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.**

Study Characteristics

All included studies were conducted in Asia: five studies were based in India[27,30-33] and one in Bangladesh[15]. Randomized trials sample size ranged from 700[30] to 26,385 participants[27]. Only one study reported the mean age of participants, indicating they were close to 30 years of age[15]. Studies followed participants from two years to six years (Table 1).

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

Author, year	Design of RCT	Country	Setting	Number of randomized participants	Mean age per studied group	Gender (male %)	Inclusion criteria	Exclusion criteria	Follow-up (years)
Feenstra 2012 [15]	RCT cluster	Bangladesh	Districts Rangpur and Nilphamari.	21,711	I: 31.5[€] P: 29.9[€]	I: 23.1 P: 23	All close contacts (were either sharing de house or kitchen with the patient, were next door neighbors, neighbors of neighbors or social contacts that stayed in the same room with the patient for at least four hours a day during a minimum of 5 days a week) of patient with leprosy.	Any person who refuses informed consent; any woman indicating that she is pregnant; any person currently on TB or leprosy treatment; missing BCG data; any person below 5 years of age; any person known to suffer from liver disease or jaundice; any person residing temporarily in the area; any person suffering from leprosy at the initial survey (these patients will be referred to the clinic for leprosy treatment); any person who is a contact of another (COLEP) patient and is already enrolled in the contact group of the other patient.	6
Neelan 1986 [30]	Parallel RCT	India	Madras city (Tamil Nadu state).	700	NR	52,5	Household contacts (children in the age group 1-15 years) of active multibacillary leprosy patients.	NR	4.7
Noordeen 1978 [31]	Parallel RCT	India	Sriperumbudur Taluk Chengalpattu district (Tamil Nadu state).	955	NR	NR	Contacts of leprosy patients (cases belonging to lepromatous types).	NR	6
Noordeen 1976 [32]	Parallel RCT	India	Chingleput district. (Tamil Nadu state).	2,000	NR	NR	Contacts of leprosy patients (cases belonging to non-lepromatous types).	NR	3.5
Wardekar 1969 [27]	RCT cluster	India	Small area near Chilakalapalli, about 14 miles from Bobbili (Andhra Pradesh state).	26,385*	NR	NR	Contacts of leprosy patients (lepromatous participants and non-lepromatous contacts cases < 25 years of age. The authors also considered newcomers < 25 years of age or newly born as part of the	NR	4.5

							sample size of the study).		
Dharmendra 1965 [33]	Parallel RCT	India	Chingleput district (Tamil Nadu state).	732	NR	55	Intrafamilial healthy child contacts of lepromatous cases and other bacteriologically positive cases of leprosy; < 15 years old who were contacts of a case within their families.	NR	2.3

I: intervention group; NR: not reported; P: placebo; COLEP: epidemiological study on contact transmission and chemoprophylaxis in leprosy; TB: tuberculosis.
[6]The mean age was based on the mean age from each group reported in the Feenstra 2012 study [15].
*From 54 villages.

All included studies used placebo as the control group. Four RCTs used dapsone[27,31-33], one RCT used acedapsone[30], and RCT trial used rifampicin[15] (Table 2).

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

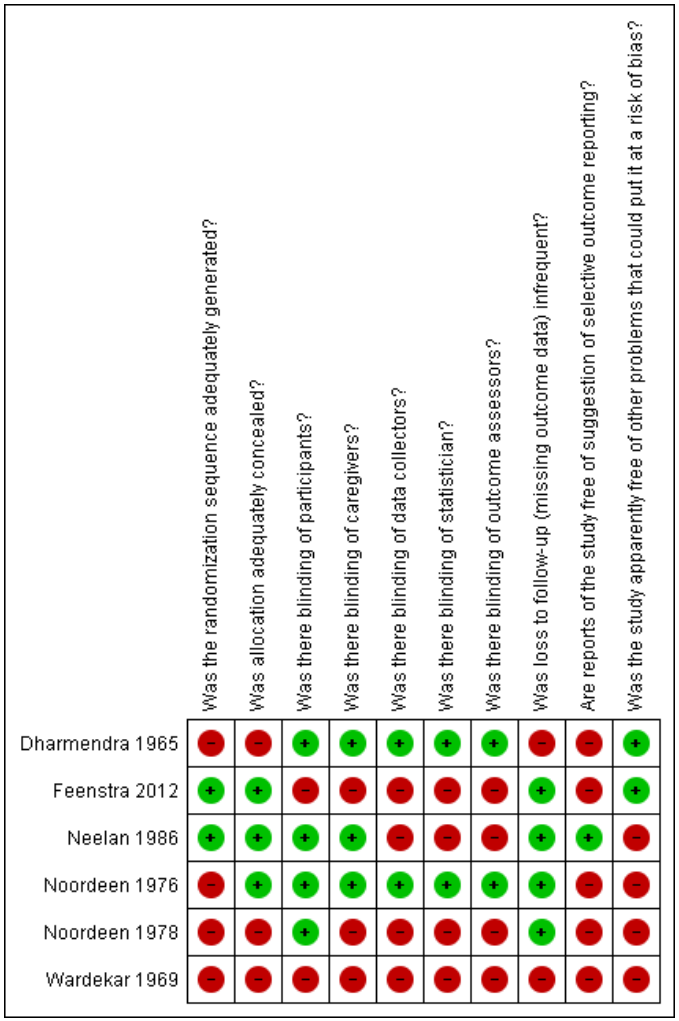
Author, year	No. of randomized patients in intervention and control	Description of intervention	Description of control	Measured outcomes
Feenstra 2012 [15]	I: 10,857 P: 10,854	Single dose rifampicin 600 mg for adults weighing 35 kg and over, 450 mg for adults weighing < 35 kg and for children > 9 years, and 300mg for children aged 5-9 years.Time: 1 day.€	Placebo.	Development of clinical leprosy; identify patient related factors. Predicting the development of new cases among their contacts and effectiveness of SDR prophylaxis.
Neelan 1986 [30]	I: 350 P: 350	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 (similar quantity of the vehicle in which acedapsone was suspended).	Development of clinical leprosy.

Noordeen 1978 [31]	I: 636 P: 319	Dapsone (age 1-2 years, 10mg; 3-5 years, 25mg; 6-10, 50mg; > 11 years, 75mg) once a week. Dapsone (age 1-2 years, 5mg; 3-5 years, 10mg; 6-10, 25mg; > 11 years, 50mg) once a week. Time: NR	Placebo tablets of Di-calcium phosphate once a week similar in appearance and size to dapsone tablets of 75mg, 50mg, 25mg, 10mg. Respectively for age groups > 11, 6 to 10, 3 to 5 and 1 to 2.	Development of clinical leprosy.
Noordeen 1976 [32]	I: 1,000 P: 1,000	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 were similar in appearance to the dapsone tablets.	Development of clinical leprosy.
Wardekar 1969 [27]	I: 13,061* P: 13,324*	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 [33]	I: 368 P: 364	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 were similar in appearance to the dapsone tablets.	Development of clinical leprosy.

I: intervention group; P: placebo; 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.
*From 27 villages.

Risk of Bias Assessment

The major issue regarding risk of bias across the included RCTs was the of selective outcome reporting[15,27,31-33]. Additionally, four studies were rated as high risk of bias for limitations in blinding of data collectors[15,27,30,31], and three studies were rated as such for limitations in allocation concealment[27,31,33] (Figure 2; Table 3).



*After four years the Feenstra 2012 study was unblinded.

Figure 2. Risk of bias assessment

Table 3. Risk of bias assessment for the randomized controlled trials.

Author, year	Was the randomization sequence adequately generated?	Was allocation adequately concealed?	Was there blinding of participants?	Was there blinding of caregivers?	Was there blinding of data collectors?	Was there blinding of statistician?	Was there blinding of outcome assessors?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?
Feenstra 2012 [15]	Definitely yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely yes	Definitely no	Probably yes
Neelan 1986 [30]	Definitely yes	Definitely yes	Probably yes	Probably yes	Probably no	Probably no	Probably no	Definitely yes	Definitely yes	Probably no
Noordeen 1978 [31]	Probably no	Probably no	Definitely yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Definitely no	Probably no
Noordeen 1976 [32]	Probably no	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely no	Probably no
Wardekar 1969 [27]	Probably no	Probably no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Probably no	Definitely no	Probably no
Dharmendra 1965 [33]	Definitely no	Definitely no	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Probably yes	Definitely no	Definitely no	Probably yes

*Defined as less than 20% loss to outcome data.
All answers as: definitely yes (low risk of bias), probably yes, probably no, definitely no (high risk of bias).

Outcomes

Meta-analysis of clinical leprosy in contacts up to two years follow-up.

Pooled results from two RCTs[15,27] 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 3). Certainty in evidence was rated down to low because of risk of bias and inconsistency, missing outcome data[27], lack of selective outcome reporting[15,27] and lack of blinding of participants[27], caregivers[27], data collectors[27], statistician[27] and outcome assessors[27] (Figure 3, Tables 3 and 4).

Meta-analysis of clinical leprosy in contacts two to five years follow-up, inclusive.

Pooled results from five RCTs[15,27,30,32,33] 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) (Figure 4). Certainty in evidence was rated down to low because of risk of bias and inconsistency, missing outcome data[27,33], lack of selective outcome reporting[15,27,32,33] and lack of blinding of participants[15,27], caregivers[15,27], data collectors[15,27,30], statistician[15,27,30] and outcome assessors[15,27,30] (Figure 3, Tables 3 and 4).

Meta-analysis of clinical leprosy in contacts > five years follow-up.

Pooled results from two RCTs[15,31] 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 5). Certainty in evidence was rated down to low because of imprecision and risk of bias, lack of selective outcome reporting[15,31] and lack of blinding of participants[15], caregivers[15,31], data collectors[15,31], statistician[15,31] and outcome assessors[15.31] (Figure 3, Tables 3 and 4).

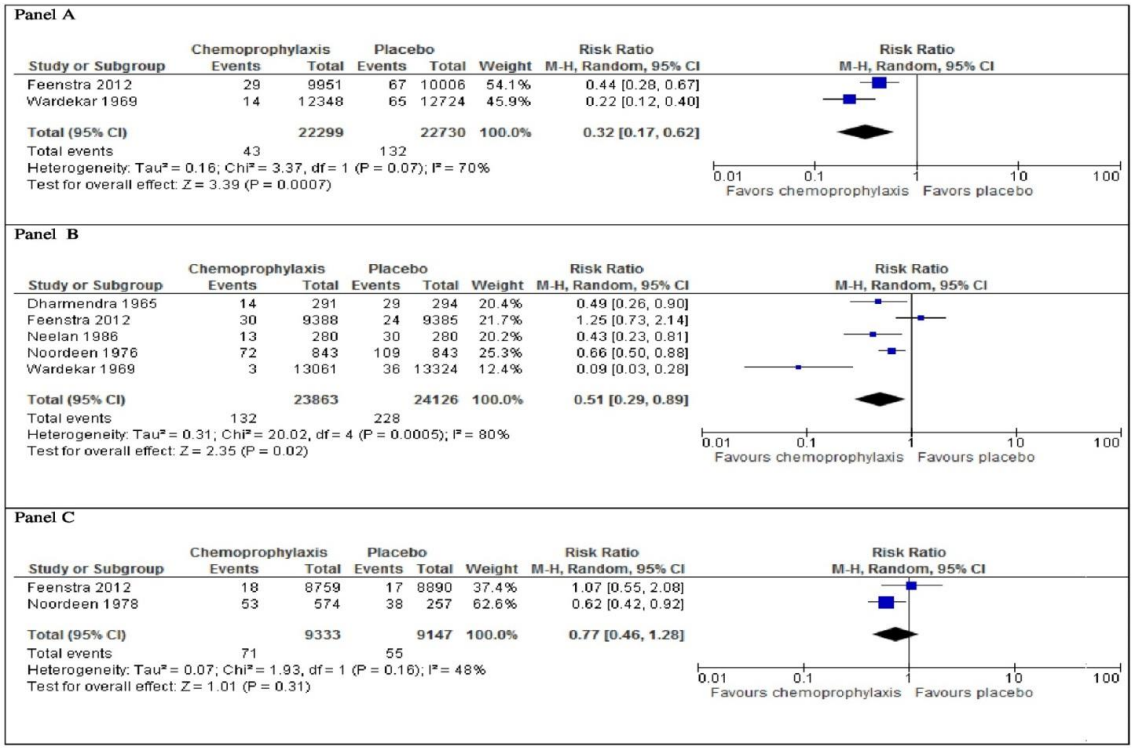


Figure 3. Meta-analysis of clinical leprosy in contacts. Panel A: Meta-analysis of clinical leprosy in contacts up to two years follow-up. Panel B: Meta-analysis of clinical leprosy in contacts two years to five years follow-up, inclusive. Panel C: Meta-analysis of clinical leprosy in contacts > five years follow-up.

Meta-analysis 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[15] and Wardekar 1969[27] 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) (Figure 4). The 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[30,32,33] 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). Certainty in evidence was rated down to moderade because of risk of bias, missing outcome data[30,33,] lack of selective outcome reporting[32,33] and lack of blinding of data collectors[30], statistician[30] and outcome assessors[30] (Figure 4, Tables 3 and 4).

Meta-analysis of clinical leprosy in contacts with only dapsone, regardless of the follow-up periods.

Pooled results from three RCTs[31-33] 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; I^2=0%, p=0.68 NNT = 22). Certainty in evidence was rated down to moderate because of risk of bias, missing outcome data[33], lack of selective outcome reporting[31-33] and lack of blinding of caregivers[31], data collectors[31], statistician[31] and outcome assessors[31] (Figure 4, Tables 3).

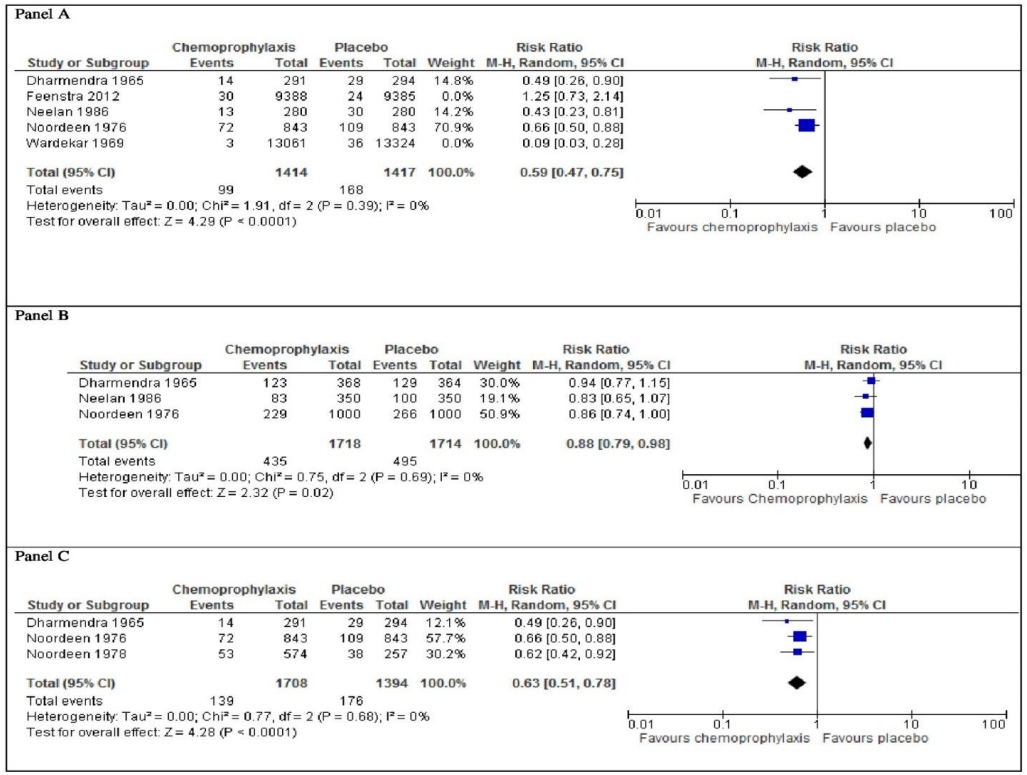


Figure 4. Sensitivity analysis of clinical leprosy in contacts. Panel A sensitivity analysis of clinical leprosy in contacts two years to five years follow-up, inclusive, excluding Feenstra 2012 and Wardekar 1969. Panel B meta-analysis of clinical leprosy in contacts two years to five years follow-up (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.

Only one included study[30] reported on adverse events, however no patients experienced it.

Table 4. GRADE evidence profile: chemophophylaxis to prevent clinical leprosy in contacts.

Quality assessment						**Summary of findings**					**Certainty in estimates**
						Study event rates		**Relative risk**	**Anticipated absolute effects over 6-12 months**		**OR**
No of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Placebo***	**Chemophophylaxis**	**(95% CI)**	**Placebo***	**Chemophophylaxis**	**Quality of evidence**
Clinical leprosy in contacts up to 2 years											
45,029 (2)[15,27]	Serious limitations[1]	Serious limitations[2]	No serious limitations	No serious limitations	Undetected	132/22,730	43/22,299	**0.32** (0.17-0.62)	7 per 1000	5 fewer per 1000 (6 fewer to 3 fewer)	LOW
Clinical leprosy in contacts from 2 to 5 years											
47,989 (5)[15,27,30,32,33]	Serious limitations[1]	Serious limitations[2]	No serious limitations	No serious limitations	Undetected	228/24,126	132/23,863	**0.51** (0.29-0.89)	129 per 1000	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)[30,32,33]	Serious limitations[1]	No serious limitations	No serious limitations	No serious limitations	Undetected	495/1,714	435/1,718	**0.88** (0.79-0.98)	266 per 1000	234 fewer per 1000 (54 fewer to 5 fewer)	MODERADE
Clinical leprosy in contacts over 5 years											
18,480 (2)[15,31]	Serious limitations[1]	No serious limitations	No serious limitations	Serious limitations[3]	Undetected	55/9,147	71/9,333	**0.77** (0.46-1.28)	148 per 1000	34 fewer per 1000 (80 fewer to 41 more)	LOW
Adverse effects											
Outcome not reported						Outcome not reported		Not estimable	Not estimable		VERY LOW

[*]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.

DISCUSSION

Main findings

Leprosy is no longer a 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[34,35]. However, the number of new cases in endemic countries remains high, and continues to rise in continents such as Africa and Asia, also affecting the pediatric population. Delayed or missed diagnoses of contagious index cases and inadequate adherence to treatment are likely significant contributors in this regard[7.]

The results of this review suggest that transmission rates among contacts of leprosy patients may be reduced with the preventive use of chemoprophylaxis, with more clear evidence up to five years. 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.[10]

While Feenstra 2012[15] and Wardekar 1969[27] 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 favouring chemoprevention, 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[27,30,32,33]. 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 resistance.

Relation to prior work

The results of our review are consistent with the findings of previous reviews[12,13,14] 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 Feenstra 2012 study with 17,649 participants[15]. A recent review presented only partial data from participants in the intervention arms of the Nordeen 1978 RCT[30], which has been fully presented here[14].

Recent literature recommends the Leprosy Post-Exposure Prophylaxis (LPEP) strategy with single-dose rifampicin (SDR) as a blanket approach to chemoprophylaxis for leprosy contacts[36,37]. 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[38,39]. Feenstra and colleagues have shown that single-dose rifampicin is effective for disease prevention[15]. The regimen is particularly effective in combination with the BCG vaccine[40]. Oo and colleagues have similarly advocated for single-dose rifampicin, but have recommended combination with ofloxacin and minocycline for appropriate prophylaxis[41].

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[37]. A Cambodian retrospective cohort study[37] and MALTELEP study[42] are similar in nature, the latter evaluating whether the BCG vaccine plus rifampicin are effective in combination for prophylaxis[42].

Discourse regarding drug resistance concerns has been varied. There is some suggestion that resistance is minimal for tuberculosis and leprosy prophylaxis, and as such, that benefits of reduced leprosy risk significantly outweigh resistance risks for tuberculosis[37,43]. 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[43].

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[44]. 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[44,45,46].

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 well-tolerated and safe[30]. 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 for leprosy. Here, we considered NNT < 25 of great relevance, NNT 25-50 of moderate relevance and 50-100 of small relevance. 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[47]. 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.

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 in children.[48]. Given its high transmissibility and social, economic, health and quality of life burdens[49], eradication of leprosy and reduction in its transmission represent fundamental public health challenges internationally.

Low-quality evidence shows that chemoprophylaxis is effective in the reduction of clinical leprosy in contacts up to two year and from two to five years follow-up. However, low-quality 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 resistance rates. Comparison of therapeutic regimens is also limited and is necessary to guide recommendations of appropriate chemoprophylaxis moving forward.

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FIGURE LEGENDS

Figure 1. Flowchart of the review.

Figure 2. Risk of bias assessment.

Figure 3. 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.

Figure 4. 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.

Table 1. Study characteristics related to population.

Table 2. Study characteristics related to description of intervention, control and outcomes.

Table 3. Risk of bias assessment for the randomized controlled trials.

Table 4. GRADE evidence profile: chemophophylaxis to prevent clinical leprosy in contacts.

Appendix Table 1. Search strategy.

Appendix Table 2. Information about contact with authors of the included studies.