Chemoprophylaxis in contacts of patients with leprosy: systematic review and meta-analysis

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ABSTRACT

Objective.   *To identify and summarize randomized clinical trials (RCTs) that assessed the effectiveness of chemoprophylaxis to prevent leprosy in contacts of patients newly diagnosed with the disease.*

Methods.   *All studies were extracted from Medline (PubMed 1966 to November 2008), the Cochrane Controlled Trials Register (number 3 2008), LILACS (1982 to November 2008), and Scirus (November 2008). Manual searches and searches of crossed references of assessed articles were also done. RCTs' risk of bias was assessed according to the methodology proposed by the Cochrane Collaboration. The main outcome measure was diagnosis of leprosy (secondary cases) in contacts of patients with the disease (primary cases).*

Results.   *The search identified 320 references, from which 7 RCTs with a total of 66 311 participants were included and evaluated. The combined results from the RCTs favored chemoprophylaxis to placebo with 2–4 years of follow-up (6 RCTs, 66 107 participants, relative risk (RR) 0.59, 95% confidence interval (CI) 0.50–0.70, I^2 = 0 (I^2 describes percent total variation across studies caused by heterogeneity)). Single-dose rifampicin (21 711 participants, RR 0.43, 95% CI 0.28–0.67, number needed to treat 285), dapsone once or twice weekly for at least 2 years (3 RCTs, 43 137 participants, RR 0.60, 95% CI 0.48–0.76, I^2 = 0), and acedapsone every 10 weeks for 7 months (2 RCTs, 1 259 participants, RR 0.49, 95% CI 0.33–0.72, I^2 = 0) were significantly superior to placebo in preventing secondary cases of leprosy.*

Conclusion.   *Chemoprophylaxis is effective in lowering the incidence of leprosy in contacts of patients diagnosed with the disease.*

Key words   Leprosy; chemoprophylaxis; contact tracing; randomized clinical trials; meta-analysis.

Leprosy is an infectious disease caused by *Mycobacterium leprae*. The main clinical manifestations include disfiguring skin sores, nerve damage, and progressive debilitation. Leprosy has two common forms, tuberculoid and lepromatous, both of which produce skin lesions. Lepromatous leprosy is the most severe form, causing generalized disease, usually with numerous papules, nodules, or plaques containing abundant *M. leprae* and affecting wide areas of skin. Diagnosis is commonly based on clinical signs and symptoms (1).

Since 1981, with the introduction of multidrug therapy by the World Health Organization (1), there has been a marked reduction in the prevalence of leprosy around the world (2, 3). The global registered prevalence of leprosy at the beginning of 2008 was 212 802 cases, and the number of new cases detected during 2007 was 254 525. The number of new cases decreased by 4.0% (11 100 cases) in 2007 compared with 2006 (4). In 1991, the World Health Organization set

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a goal to eliminate leprosy as a public health problem, initially by the year 2000 (3) and then extending it to 2005 (5). The aim was to reduce global and national prevalence to 1 case per 10 000. Angola, Brazil, Central African Republic, Democratic Republic of Congo, India, Madagascar, Mozambique, Nepal, and the United Republic of Tanzania remain high endemic areas (4).

Despite a progressive decline in cases of leprosy registered in the last 20 years, it has not been possible to eliminate the disease—measured as complete interruption of transmission, incidence reduction to zero (6), and suppression of every source of infection (7).

One strategy required to reach this goal is to address treatment to high-risk groups, which are the source of active transmission of the disease (8, 9). Beginning in the 1940s, dapsone was the drug of choice to treat leprosy until it was replaced by a modality of multidrug therapy that included a combination of dapsone, clofamizine, and rifampicin. In the 1960s, chemoprophylaxis for contacts of patients with leprosy was introduced.

One systematic review and meta-analysis published in 2000 (a review that pooled two duplicated studies) found that prolonged administration of dapsone and acedapsone could prevent leprosy development in contacts by 40.0% to 60.0% compared with placebo (10). Nevertheless, those treatments are characterized by low adherence because of the need for prolonged administration (11). More recent studies evaluating the role of other treatments with shorter administration times have been published (12–14).

The aim of this study is to review systematically the information provided by randomized clinical trials (RCTs) on the effectiveness of chemoprophylaxis to prevent leprosy among patients' contacts.

MATERIALS AND METHODS

Literature search

Structured searches were conducted in PubMed (1966 to November 30, 2008), the Cochrane Controlled Trials Register (number 3 2008), and LILACS (1982 to November 30, 2008). The following terms were used and adapted for each database (15, 16): leprosy, leprosies, Hansen, leprotic, leprae, lepra and chemoprophy-

laxis, contact*, families, family, relative*, prophylaxis, chemoprevention. The *meta* Register of Controlled Trials (www.controlled-trials.com), clinicaltrials.gov, Clinical Trials Registry–India (http://www.ctri.in/), the Latin American Clinical Trials Register (www.latinrec.org), and the International Clinical Trials Registry Platform search portal of the World Health Organization (http://www.who.int/trialsearch/) were also searched for ongoing trials. We completed a search in Scirus (limits: medicine; November 30, 2008) to identify studies published in ScienceDirect, BioMed Central, and other databases. Additional searches were done in crossed references of assessed articles, reviews, and textbooks related to Hansen disease. A manual search was performed in the *International Journal of Leprosy and Other Mycobacterial Diseases* (1960–2007), *Leprosy in India*, and *Leprosy Review* (1960–1983) according to methodology suggested for the Cochrane Collaboration manual (17). When possible, we directly contacted authors to review unpublished studies and additional data from manuscripts.

Study selection

The titles, abstracts, and studies identified in the literature search were assessed separately by two independent reviewers. All trials matching the inclusion criteria were reviewed by at least two authors. Disagreements between reviewers were resolved by referring to a third author when necessary. Only RCTs using chemoprophylaxis of contacts were considered in the review compared with no intervention, placebo, or other chemoprophylaxis schemes. We excluded those studies in which the intervention group included vaccines.

Data extraction

Two reviewers (L.R. and J.A.B.) independently extracted the relevant data using a predesigned data extraction form; disagreements were resolved by consensus of all authors. The most relevant variables extracted from studies were identification data of the paper, treatment characteristics (type of intervention, dose, and duration), demographic variables, number of participants, losses, proportion of patients with clinical diagnosis of leprosy (secondary cases), how diagnosis was made, and

adverse events. For analysis of the type and frequency of adverse effects, we used included and excluded studies when possible.

A risk of evaluation bias of each RCT was performed and included details of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other issues" following the Cochrane Collaboration tool for the assessment of these features (8). Additional quality information included inclusion and exclusion criteria; sample size calculation; and baseline comparability of age, gender, relevant clinical characteristics, and diagnoses (17–19). Data were registered in the studies table (Table 1).

Differences were discussed for each pair of reviewers, and disagreements were discussed between two researchers who did not know the information obtained as a result of selected article review. Data on outcomes were obtained directly from articles and were compared with the Review Manager Version 5.0 (RevMan 5) program.

Definitions and outcomes

Any method to diagnose leprosy was permitted. Clinical diagnosis of leprosy (secondary cases) was the main outcome considered. We used data on adverse events only from included RCTs; no further searches for other types of studies were done.

Statistical analysis

Statistical analyses were done with RevMan 5 (Cochrane Collaboration) software. The results, expressed as relative risk (RR) and 95% confidence intervals (CI) for dichotomous primary outcomes, were calculated by the Mantel–Haenszel random effects model. Weighted mean difference with a 95% CI was used for continuous outcomes. For the pooled analysis, we calculated the I^2 statistic, which describes the percentage of total variation across studies caused by heterogeneity (17). Low, moderate, and high levels of heterogeneity approximately correspond to I^2 values of 25%, 50%, and 75%, respectively. Within the analysis, we considered as possible sources of heterogeneity differences between diagnostic criteria, gender proportions, age, geographic areas, drug dosages, and quality of studies.

TABLE 1. Main characteristics of included randomized clinical trials

Study	Methods	Participants	Interventions	Outcomes
Moet et al. 2008 (38)	Double-blind randomized clinical trial. Generation and concealment of randomizing sequence using computer. Cluster randomization according to index patient. Follow-up from 24 to 40 months. Follow-up losses 7.7% between 1 and 2 years and 13.1% between 3 and 4 years.	21 711 contacts of 1 037 patients with incident cases from which 400 paucibacillary cases had one lesion, 380 had two to five lesions, and 295 had multibacillary leprosy. Six categories of physical contact (house and kitchen sharing, kitchen only, house only, close neighbor, neighbor of neighbor, social contact for at least 4 hours 5 days a week) and two from genetic proximity (close (sons, parents, brother) and not close). Pregnant women treated for tuberculosis and leprosy, under 5 years, with hepatic diseases, temporal residents, and positive for anti-phenolic glycolipid I IgM by ELISA.[a]	Posterior to second standard dose of treatment of index case was started in controls. Rifampicin, two to four 150-mg[b] capsules according to body mass index and age. Identical placebo.	Primary: clinical presence of leprosy between first and second year and between third and fourth year. No data on adverse events.
Oo et al. 2008 (39)	Randomized controlled trial. Blinded only for patients. Sequence generation and concealment by computer. Placebo similar in appearance to intervention treatment. No losses in first year of follow-up; 13.3% losses in follow-up until second year. No reported measures to ensure treatment adherence.	300 seropositive contacts for anti-phenolic glycolipid I IgM by ELISA reported as new cases in Nianmar. In each intervention group, there were 102 adults and 48 children. Leprosy cases were diagnosed according to World Health Organization classification. People who lived in the same house and neighbors within three houses were included.	Adults: rifampicin at 600 mg, ofloxacine at 400 mg, and minocycline at 100 mg. Children less than 15 years old: rifampicin, one dose only at 25 mg per kg[c] of body weight. Placebo consisted of vitamins of similar appearance to treatment.	Primary: anti-phenolic glycolipid I IgM by ELISA for leprosy average titer for 1 and 2 years follow-up. No data on adverse events.
Wardekar 1967 (40)	Randomized double-blind controlled trial. Generation and concealment of sequence unclear. 27 villages randomized to dapsone and 27 to placebo. Not clear if blinding was successful because placebo had a distinctive appearance. Losses were reported as 5% first year until 2 years follow-up.	The whole population of 52 villages in India.	Dose of dapsone every 2 weeks for 2 years. Dose according to age range: 0–2 years, 20 mg; 3–5 years, 40 mg; 6–10 years, 100 mg; 11–15 years, 150 mg; 16–25 years, 300 mg.	Primary: clinical presence of leprosy between 10 and 21 months and between 23 and 31 months once treatment initiated.
Noordeen 1969 (41) Noordeen 1977 (21)	Double-blind randomized controlled trial. Generation and concealment of sequence unclear. Patients were randomized after stratification by age and sex.	700 children less than 15 years old in contact with patients with lepromatous form of leprosy or bacteriologically positive. Published in 1969 to 4.5 years follow-up and published again until 8.5 years follow-up.	Oral dapsone (10–75 mg) twice a week for 3 years after index case was reported as negative.	Primary: clinical presence of leprosy.
Noordeen and Neelan 1978 (42)	Double-blind randomized controlled trial. Not clear how sequence generation and concealment were done. 318 were randomized to dapsone at 75 mg, 318 to dapsone at 50 mg, and 319 to placebo. 12% loss to follow-up was reported during 6-year follow-up.	955 children contacts of lepromatous leprosy and 2 000 of nonlepromatous leprosy were identified through survey in Sriperum-budur, India.	Usual dose group: dapsone weekly dose for 2 years. Dose according to age range: 0–2 years, 10 mg; 3–5 years, 25 mg; 6–10 years, 50 mg; 11–15 years, 75 mg. Low-dose group: dapsone weekly dose for 2 years. Dose according to age range: 0–2 years, 5 mg; 3–5 years, 10 mg; 6–10 years, 25 mg; 11–15 years, 50 mg. Placebo.	Primary: clinical presence of leprosy between 12 and 24 months of initiated treatment.

(continued)

TABLE 1. (Continuation)

Study	Methods	Participants	Interventions	Outcomes
Neelan et al. 1983 (43)	Double-blind controlled clinical randomized trial. Not clear how sequence generation and concealment were done. 11% lost to follow-up for 3.5 years.	399 children contacts of patients with active multibacillary leprosy and under treatment. Performed in eight centers in Madras, India.	Acedapsone dose every 10 weeks for 7 months. Dose according to age range: 1–5 years, 150 mg; 6–14 years, 225 mg.	Primary: clinical presence of leprosy evaluated every 10th week during treatment and until end of study.
Neelan et al. 1986 (44)	Double-blind controlled clinical randomized trial. Not clear how sequence generation and concealment were done. No loss to follow-up reported during 225 weeks or 4.5 years of follow-up.	560 contacts of patients with multibacillary active leprosy and under treatment in eight clinical centers in Madras, India.	Acedapsone dose every 10 weeks for 7 months. Dose according to age range: 1–5 years, 150 mg; 6–14 years, 225 mg.	Primary: clinical presence of leprosy at 10th, 13th, and 26th week of initiated treatment.

[a] ELISA = enzyme-linked immunosorbent assay.
[b] mg = milligram.
[c] kg = kilogram.

TABLE 2. Assessment of bias risk of randomized clinical trials[a]

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel, and outcome assessors	Incomplete outcome data and withdrawals	Free of selective reporting?	Other sources of bias and commentaries	Overall assessment
Moet et al. 2008 (38)	Yes[b]	Yes	Yes	Yes	Yes	Yes	Yes
Oo et al. 2008 (39)	Yes	Yes	No[c]	Yes	Unclear	Unclear	Unclear
Wardekar 1967 (40)	Unclear	Unclear	Inadequate	Unclear	Unclear	Unclear	Unclear
Noordeen 1969 (41)	Unclear	Unclear	Unclear	No	Unclear	Yes	Unclear
Noordeen and Neelan 1978 (42)	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear
Neelan et al. 1983 (43)	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear
Neelan et al. 1986 (44)	Unclear	Unclear	Yes	Yes ND[d]	Yes	Yes	Unclear

[a] According to the Cochrane Collaboration Handbook:
  Sequence generation: Was the allocation sequence adequately generated?
  Allocation concealment: Was allocation adequately concealed?
  Blinding of participants, personnel, and outcome assessors: Was knowledge of the allocated intervention adequately prevented during the study?
  Incomplete outcome data and withdrawals: Were intention-to-treat analyses performed? Had participants withdrawn from the study?
  Free of selective reporting?
  Other sources of bias and commentaries: Was sample size calculated? Were inclusion and exclusion criteria and baseline characteristics defined? Were conflicts of interest reported?
[b] Yes = low risk of bias.
[c] No = high risk of bias.
[d] ND = no dropouts.

RESULTS

Characteristics of studies

The literature search identified more than 320 references of interest, mainly in PubMed and the Cochrane Controlled Trials Register. LILACS (Latin American database), manual searches, Scirus, and ongoing registries did not provide any additional RCTs. We selected 29 relevant studies of chemoprophylaxis of contacts of patients diagnosed with leprosy. From this group, 22 did not comply strictly with eligibility criteria and were excluded because they were nonrandomized or noncontrolled trials (14, 20–37). We included and analyzed a total of 7 RCTs with 66 311 participants

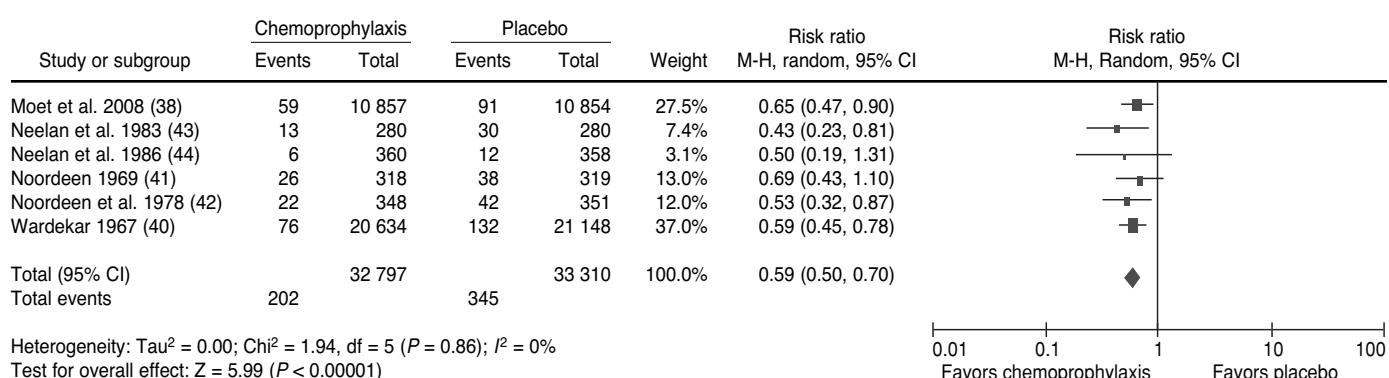(38–44); however, only 6 RCTs provided clinical data (38, 40–44).

The main characteristics of included studies are reported in Table 1. From the seven RCTs, two were published in the 1960s, one in the 1970s, two in the 1980s, and two in the last 10 years; all were carried out in Asia. Regarding leprosy diagnosis, most studies applied clinical criteria frequently, including the presence of at least one cardinal symptom of the disease—that is, cutaneous erythematous or hypopigmented anesthesic lesions and thickening of peripheral nerves associated with sensitive or motor alterations from innervated territories; positive bacilloscopy in slit skin smears was also used. Most RCTs included close contacts of leprosy patients (41, 43, 44) or both household and community contacts (38, 39, 42). Only one study, of 52 villages in India, included the whole population (40).

Only two of the RCTs (38, 39) reported the type of disease in the primary case, discriminating between paucibacillary leprosy (one lesion, between two and five lesions) and multibacillary leprosy. Most studies reported a follow-up time of at least 2 years and a maximum of 8.5 years.

Assessment of risk of bias

Table 2 shows the assessment of risk of bias of included studies according to the Cochrane Collaboration manual (19). Most RCTS were judged as having an unclear risk bias. We found only one RCT with low risk of bias (38). Generation and con-

FIGURE 1. Meta-analysis of chemoprophylaxis with dapsone, rifampicin, and acedapsone compared with placebo: M-H = Mantel–Haenszel, CI = confidence interval, df = degrees of freedom

Study or subgroup	Chemoprophylaxis Events	Chemoprophylaxis Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, random, 95% CI	Risk ratio M-H, Random, 95% CI
Moet et al. 2008 (38)	59	10 857	91	10 854	27.5%	0.65 (0.47, 0.90)	
Neelan et al. 1983 (43)	13	280	30	280	7.4%	0.43 (0.23, 0.81)	
Neelan et al. 1986 (44)	6	360	12	358	3.1%	0.50 (0.19, 1.31)	
Noordeen 1969 (41)	26	318	38	319	13.0%	0.69 (0.43, 1.10)	
Noordeen et al. 1978 (42)	22	348	42	351	12.0%	0.53 (0.32, 0.87)	
Wardekar 1967 (40)	76	20 634	132	21 148	37.0%	0.59 (0.45, 0.78)	
Total (95% CI)		32 797		33 310	100.0%	0.59 (0.50, 0.70)	
Total events	202		345				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.94, df = 5 (P = 0.86); I^2 = 0%
Test for overall effect: Z = 5.99 (P < 0.00001)

0.01　0.1　1　10　100
Favors chemoprophylaxis　　Favors placebo

TABLE 3. Main outcomes of randomized clinical trials

Study	Main outcome	Intervention	Comparator	Estimate (95% CI)[a]
Moet et al. 2008 (38)	Diagnosis of new case of leprosy at 4 years.	Rifampicin	Placebo	RR[b] 0.65 (0.47–0.90)
Oo et al. 2008 (39)	Mean difference before and after 2 years of anti-phenolic glycolipid I IgM by ELISA[c] for leprosy average titer.	Adults: rifampicin, ofloxacine, and minocycline Children: rifampicin	Placebo	Adults: MD[d] 0.06 (0.04–0.08) Children: MD 0.04 (0.01–0.09)
Wardekar 1967 (40)	Diagnosis of new case of leprosy between 23 and 31 months of initiated treatment.	Dapsone	Placebo	RR 0.59 (0.45–0.78)
Noordeen 1969 (41)	Diagnosis of new case of leprosy at 4.5 and 8.5 years.	Dapsone	Placebo	4.5 years: RR 0.50 (0.19–1.31) 8.5 years: RR 0.52 (0.24–1.11)
Noordeen and Neelan 1978 (42)	Clinical presence of leprosy between 12 and 24 months of initiated treatment.	Dapsone usual dose Dapsone low dose	Placebo	Contacts of lepromatous patients: treatment group Usual dose: RR 0.68 (0.42–1.10) Low dose: RR 0.71 (0.44–1.13) Contacts of nonlepromatous patients: RR 0.66 (0.49–0.87)
Neelan et al. 1983 (43)	Clinical presence of leprosy between 12 and 24 months of initiated treatment.	Acedapsone	Placebo	RR 0.55 (0.33–0.91)
Neelan et al. 1986 (44)	Clinical presence of leprosy between 12 and 24 months of initiated treatment.	Acedapsone	Placebo	RR 0.45 (0.24–0.86)

[a] CI = confidence interval.
[b] RR = relative risk.
[c] ELISA = enzyme-linked immunosorbent assay.
[d] MD = mean difference.

cealment of sequence were reported adequately in two of seven studies (38, 39). Staff and participant blinding was done in four of seven studies (38, 42–44). Table 1 shows losses to follow-up for each RCT.

Quantitative synthesis

Meta-analysis of the incidence of new cases of leprosy in contacts of patients was performed on an intention-to-treat (ITT) basis. D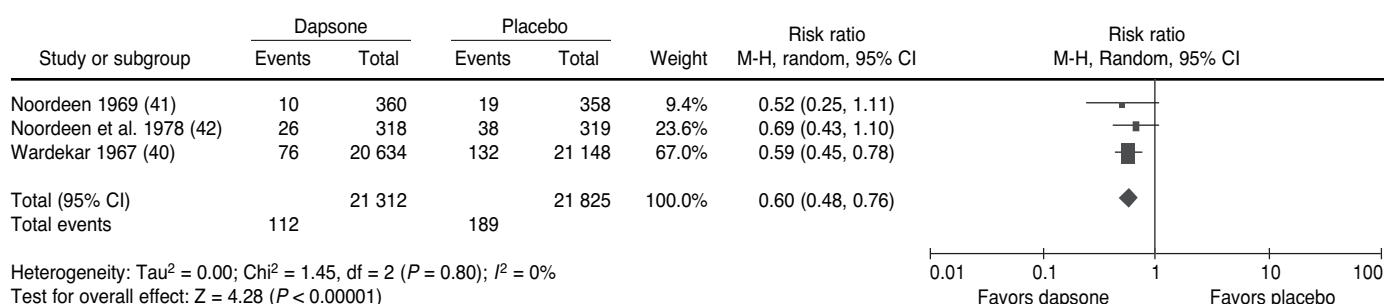ata on all treatments compared with placebo were pooled. Summary measures favored chemoprophylaxis over placebo at 2 and 4 years of follow-up (6 RCTs, 66 107 participants, RR 0.59, 95% CI 0.50–0.70; I^2 = 0) (Figure 1). Table 3 describes the results for the main outcome.

Rifampicin

Two RCTs in which rifampicin was used were reviewed (38, 39). Moet et al. (38) looked at the effectiveness of single-dose rifampicin compared with placebo.

They found chemoprophylaxis with rifampicin to be significantly better than placebo at preventing the occurrence of new cases of leprosy at 2 and 4 years of follow-up (ITT 21 711 participants, RR 0.43, 95% CI 0.28–0.67, number needed to treat (NNT) 285 and RR 0.65, 95% CI 0.47–0.90, NNT 339, respectively). Nevertheless, no statistically significant differences were found when the time period between the third and fourth year of follow-up was included (ITT 21 711 participants, RR 1.25, 95% CI 0.73–2.14).

FIGURE 2. Meta-analysis of chemoprophylaxis with dapsone compared with placebo: M-H = Mantel–Haenszel, CI = confidence interval, df = degrees of freedom

Study or subgroup	Dapsone		Placebo		Weight	Risk ratio M-H, random, 95% CI	Risk ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
Noordeen 1969 (41)	10	360	19	358	9.4%	0.52 (0.25, 1.11)	
Noordeen et al. 1978 (42)	26	318	38	319	23.6%	0.69 (0.43, 1.10)	
Wardekar 1967 (40)	76	20 634	132	21 148	67.0%	0.59 (0.45, 0.78)	
Total (95% CI)		21 312		21 825	100.0%	0.60 (0.48, 0.76)	
Total events	112		189				

Heterogeneity: Tau² = 0.00; Chi² = 1.45, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 4.28 (P < 0.00001)

0.01 0.1 1 10 100
Favors dapsone   Favors placebo

The overall benefit of rifampicin over placebo at 2 years of follow-up was consistent in different age ranges: 10–14 years (2 988 participants, RR 0.17, 95% CI 0.04–0.75), 20–29 years (3 254 participants, RR 0.11, 95% CI 0.01–0.82), and > 30 years (7 647 participants, RR 0.51, 95% CI 0.28–091). A benefit was also observed in relatives not so close to the contacts (15 971 participants, RR 0.33, 95% CI 0.19–0.57).

In the category of neighbors and social contacts (11 351 participants, RR 0.38, 95% CI 0.17–0.82), in men (8 697 participants, RR 0.46, 95% CI 0.26–0.81), and in women (10 172 participants, RR 0.40, 95% CI 0.21–0.79), primary individuals presented with paucibacillary leprosy (7 923 participants, RR 0.42, 95% CI 0.20–0.88) and with two to five lesions (6 541 participants, RR 0.38, 95% CI 0.17–0.82).

Finally, rifampicin was favored equally in those patients who had not had a bacillus Calmette–Guérin (BCG) vaccination (11 795 participants, RR 0.42, 95% CI 0.26–0.69) and in those whose initial enzyme-linked immunosorbent assay (ELISA) for leprosy was negative (16 169 participants, RR 0.42, 95% CI 0.26–0.69). No adverse events were reported.

Oo et al. (39) assessed leprosy only to IgM titers through ELISA. Mean differences before treatment and at 2 years of follow-up showed a significant benefit from a combination of rifampicin, ofloxacine, and minocycline compared with placebo at 2 years in adults (204 participants, mean difference 0.06, 95% CI 0.04–0.08). In children, this difference was not detected (96 participants, mean difference 0.04, 95% CI 0.01–0.09). No adverse events were reported.

Dapsone

Three studies evaluating a weekly or twice weekly dose of dapsone for at least 2 years were included (40–42). Wardekar (40) performed cluster randomization with 27 villages on dapsone and 27 villages on placebo. Dapsone was significantly superior to placebo to prevent the appearance of new cases of leprosy in the general population (ITT 41 782 participants, RR 0.59, 95% CI 0.45–0.78), especially in patients aged 25 years or younger (ITT 25 072 participants, RR 0.21, CI 95% 0.12–0.38). Dapsone was also superior to placebo in preventing the appearance of nonlepromatous leprosy in the general population (ITT 41 782 participants, RR 0.58, 95% CI 0.44–0.78). Nevertheless, the benefit of dapsone was not statistically significant in contacts aged 25 years or older or to prevent lepromatous cases of the disease. No adverse events were reported.

The study failed to report appropriate analyses for cluster RCT (i.e., intracluster correlation coefficient), and we could not find an external report to impute data.

Noorden and Neelan (42) assessed the effectiveness of dapsone at the usual dose (75 milligrams (mg)) and at a low dose (50 mg) compared with placebo in cases of lepromatous and nonlepromatous leprosy during 6 years of follow-up (22). The incidence of leprosy in contacts of patients with the lepromatous form of the disease at the usual dose was 64.7 cases per 100 000 persons per year of treatment; at low doses, it was 67.2 cases per 100 000 persons per year of treatment, and in the placebo group it was 107.2 cases per 100 000 persons per year of treatment. No statistically significant difference was found in the group of low-dose patients compared with those on placebo (RR 0.71, 95% CI 0.44–1.13) or in the group with the usual dose and placebo (RR 0.68, 95% CI 0.42–1.10). In contacts of patients with nonlepromatous leprosy, only a group taking the usual dose (75 mg) was compared with those on placebo, with statisti-cally significant differences favoring treatment (52.15 cases per 100 000 persons per year of treatment in the treatment group compared with 79.78 cases per 100 000 persons per year of treatment in the placebo group) (RR 0.66, 95% CI 0.49–0.87). No adverse events were reported.
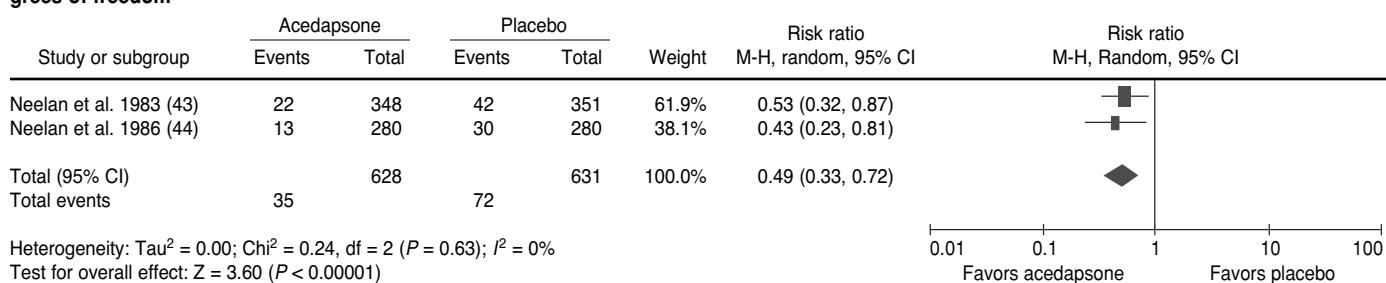
Noorden et al. (41) found in their preliminary report (20, 21) that chemoprophylaxis with dapsone was not significantly better than placebo to prevent the appearance of new cases of leprosy at 4.5 and 8.5 years of follow-up (ITT 718 participants, RR 0.50, 95% CI 0.19–1.31 and RR 0.52, 95% CI 0.25–1.11, respectively). Because of the large number of losses to follow-up, the authors reported the incidence of new cases of leprosy in contacts per person per week, finding a statistically significant difference that favored the treatment group with dapsone (31.6 cases per 100 000 persons per week versus 13.9 cases per 100 000 persons per week; P < 0.05).

Meta-analysis of these three studies significantly favored dapsone to placebo (3 RCT, 4 337 participants, RR 0.60, 95% CI 0.48–0.76, I² = 0) (Figure 2).

Acedapsone

Two studies evaluating an acedapsone dose every 10 weeks for 7 months were included (43, 44). Neelan et al. (43) assessed the efficacy of acedapsone compared with placebo in contacts of patients with multibacillary leprosy. In this study, chemoprophylaxis with acedapsone was significantly better than placebo in preventing the appearance of new cases at 3.5 years of follow-up (incidence in the treatment group was 63.2 per 1 000 versus 119.7 per 1 000 in the placebo group) (RR 0.55, 95% CI 0.33–0.91). No differences within age ranges were shown. No adverse events were reported.

FIGURE 3. Meta-analysis of chemoprophylaxis with acedapsone compared with placebo: M-H = Mantel–Haenszel, CI = confidence interval, df = degrees of freedom

Study or subgroup	Acedapsone		Placebo		Weight	Risk ratio M-H, random, 95% CI	Risk ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
Neelan et al. 1983 (43)	22	348	42	351	61.9%	0.53 (0.32, 0.87)	
Neelan et al. 1986 (44)	13	280	30	280	38.1%	0.43 (0.23, 0.81)	
Total (95% CI)		628		631	100.0%	0.49 (0.33, 0.72)	
Total events	35		72				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.24, df = 2 (P = 0.63); I^2 = 0%
Test for overall effect: Z = 3.60 (P < 0.00001)

0.01 0.1 1 10 100
Favors acedapsone   Favors placebo

Neelan et al. (44) assessed the effectiveness of acedapsone with placebo in contacts of patients with multibacillary leprosy. They found that chemoprophylaxis with acedapsone was significantly better than placebo in preventing the appearance of new cases at 4.7 years of follow-up (incidence in the treatment group was 46.4 per 1 000 versus 107.1 per 1 000 in the placebo group) (RR 0.45, 95% CI 0.24–0.86). No differences were found in children aged 9 years or younger and in groups of children aged 9 years or older (1–8 years: 132.7 cases per 1 000 persons in the control group versus 61.4 cases per 1 000 persons in the treatment group; 9 or more years: 89.8 cases per 1 000 persons in the control group versus 59.8 cases per 1 000 persons in the treatment group). No adverse events were reported.

Meta-analysis of these two studies significantly favored acedapsone to placebo (2 RCT, 1 259 participants, RR 0.49, 95% CI 0.33–0.72, I^2 = 0) (Figure 3).

DISCUSSION

We have produced updated coverage of randomized controlled trials of chemoprophylaxis for leprosy in contacts by summarizing the best available evidence using quantitative methods. We have endeavored to provide information to help clinicians and stakeholders choose the most appropriate treatment. The evidence found in this systematic review shows that the incidence of leprosy among patients' contacts can be reduced with pharmacologic treatment in the range of 30% to 72%. Acedapsone (43, 44) and rifampicin (38, 39) were more effective than placebo and also presented a significant reduction (between 67% and 57%, respectively) in the incidence of leprosy in patients' contacts. Findings were obtained from RCTs in highly endemic populations. We are un-

able to generalize these results to less endemic populations.

The results confirm the findings of a previous meta-analysis, where the authors found that prolonged administration of dapsone and acedapsone (20, 21) could prevent the appearance of leprosy among contacts by 40% to 60% compared with placebo (10). However, the previous review had several methodologic limitations, mainly due to duplication bias by including the results of Nordeen et al. (41) three times in the pooled results estimated. Therefore, the evidence provided by this review from homogenized RCTs proves the positive impact that can be obtained in leprosy burden mainly in endemic countries by using chemoprophylaxis in contacts of patients with leprosy.

A minimal reduction (30%) in the incidence of leprosy between contacts would directly affect the incidence of the disease worldwide and would significantly contribute to World Health Organization goals (1 case of leprosy per 10 000 persons), a goal that has not been obtained in countries such as Brazil and India where the rates are 4.6 and 2.4 cases per 10 000, respectively (8).

The incidence of the disease in countries where the postreduction phase is apparently taking place—such as Colombia, where the annual incidence has been about 500 cases (1.5 per 100 000 persons) since the 1990s (45)—would also tend to be reduced.

The chemoprophylactic effect appears not to be the same for all subgroups of contacts. In the COLEP study, contacts who were not closely related to the index patient or who lived further away benefited more from prophylaxis (38). In addition, the presence of a BCG scar did not affect the response to chemoprophylaxis, suggesting that BCG (one or many doses) could have an additional effect when treating with rifampicin, a finding that should be studied further (38). The

effect of chemoprophylaxis has not been assessed comparing contacts of multi- and paucibacillary forms of leprosy or adjusted estimates for distance between contacts. These issues are outside the scope of this review and should be explored further by RCTs.

We considered that assessing the effect of combined therapy would not have benefits in addition to what has been found separately given the satisfactory estimates found. Moet et al. (38) reported a significant improvement in the number of leprosy cases at 2 years but not at 4 years; it is plausible that the effectiveness and safety of periodic administration of a single dose of rifampicin could be assessed by RCTs. It is also relevant that in this study there was no significant improvement in cases of leprosy for patients less than 1 year old (38).

Limitations of this review mainly concern the methodologic quality of some of the studies included. Limiting factors include the absence of concealing randomizing sequences and the absence of reporting adverse events.

In conclusion, administration of rifampicin, acedapsone, and dapsone may reduce the incidence of leprosy in contacts of patients and should be recommended within clinical practice guidelines and public health policies.

Implications for practice

Chemopropylaxis with rifampicin, acedapsone, and dapsone may reduce the incidence of leprosy in contacts of patients. A single dose of rifampicin in contacts of patients newly diagnosed with leprosy was 57% effective at preventing the development of leprosy after 2 years.

Implications for research

Evidence suggests the importance of performing RCTs that assess the efficacy

and safety of rifampicin in periodic doses to high-risk populations that allow subgroup analyses by age, type of contact, and type of initial disease.

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RESUMEN

Quimioprofilaxis en contactos de pacientes con lepra: revisión sistemática y metanálisis

Objetivo. Identificar y hacer un compendio de los ensayos clínicos aleatorizados (ECA) que evaluaron la eficacia de la quimioprofilaxis para prevenir la lepra en los contactos de pacientes con diagnóstico reciente de esa enfermedad.

Métodos. Se extrajeron todos los estudios de Medline (PubMed, de 1966 a noviembre de 2008), el Registro de Ensayos Controlados de Cochrane (No. 3 de 2008), LILACS (de 1982 a noviembre de 2008) y Scirus (noviembre de 2008). Se hicieron búsquedas manuales y se localizaron referencias cruzadas de los artículos analizados. Se evaluó el riesgo de sesgo de los ECA de acuerdo con la metodología propuesta por la Colaboración Cochrane. El principal criterio de valoración fue el diagnóstico positivo de lepra (casos secundarios) en los contactos de pacientes con esa enfermedad (casos primarios).

Resultados. Se identificaron 320 referencias, de las cuales se evaluaron 7 ECA con un total de 66 311 participantes. Los resultados combinados de los ECA favorecieron la quimioprofilaxis frente al placebo con 2–4 años de seguimiento (6 ECA, 66 107 participantes; riesgo relativo [RR] = 0,59; intervalo de confianza de 95% [IC95%]: 0,50 a 0,70; I^2 = 0 [I^2 describe la variación porcentual total en los estudios debida a la heterogeneidad]). Una dosis única de rifampicina (21 711 participantes; RR = 0,43; IC95%: 0,28 a 0,67; número necesario a tratar: 285), dapsona una o dos veces por semana durante al menos 2 años (3 ECA, 43 137 participantes; RR = 0,60; IC95%: 0,48 a 0,76, I^2 = 0) y acedapsona cada 10 semanas durante 7 meses (2 ECA, 1 259 participantes; RR = 0,49; IC95%: 0,33 a 0,72; I^2 = 0) fueron significativamente superiores que el placebo en la prevención de casos secundarios de lepra.

Conclusiones. La quimioprofilaxis es eficaz para reducir la incidencia de lepra en los contactos de pacientes diagnosticados con esta enfermedad.

Palabras clave Lepra; quimioprevención; trazado de contacto; ensayos clínicos aleatorios; metanálisis.

AIEPI Neonatal: Intervenciones basadas en evidencia

En la Región de las Américas la mayoría de los indicadores de salud infantil y de la niñez han presentado cambios sustanciales y favorables en la mayoría de países; sin embargo, la salud neonatal ha sido olvidada y poco visualizada por parte de las autoridades de salud, lo cual ha tenido como efecto un gran énfasis en la reducción de la mortalidad post-neonatal y muy poco en la reducción de la mortalidad neonatal. Como consecuencia, actualmente más del 70% de la mortalidad infantil es producto de la mortalidad neonatal.

Los principales factores que han contribuido a la disminución de la mortalidad neonatal en los países con bajas tasas de mortalidad neonatal han sido, además de la mejoría socioeconómica y educación de los padres, el buen control del embarazo y la atención calificada del parto; la regionalización de la atención perinatal; el inicio oportuno del cuidado intensivo neonatal, y la buena atención del recién nacido en el momento del nacimiento, que incluye, en caso necesario, una adecuada e inmediata reanimación. Las intervenciones que se presentan en este documento, fueron seleccionadas en base a la evidencia científica actual y en el análisis de su factibilidad y su potencial para reducir morbilidad neonatal. Estas intervenciones pueden incluirse en un paquete de acuerdo al nivel de atención que ofrecen los sistemas de salud.

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