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

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CRD summary
This review concluded that chemoprophylaxis was effective in lowering the incidence of leprosy in contacts of patients diagnosed with the disease. This was a well-conducted review and despite the small number of trials of limited quality the findings reflected the evidence presented and are likely to be reliable. The generalisability of the findings to less endemic populations was unclear.

Authors' objectives
To assess the effectiveness of chemoprophylaxis to prevent leprosy in contacts of patients newly diagnosed with the disease.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS and Scirus were searched to November 2008. Search terms were reported. Ongoing trials were sought through searches of the Register of Controlled Trials, ClinicalTrials.gov, Clinical Trials Registry-India, Latin American Clinical Trials Register and International Clinical Trials Registry Platform search portal of the World Health Organization. Authors were approached to review unpublished trials. Manual searches of International Journal of Leprosy and Other Mycobacterial Diseases (from 1960 to 2007), Leprosy in India and Leprosy Review (from 1960 to 1983) were undertaken. Reference lists of included studies, reviews and textbooks were searched for additional articles.

Study selection
Randomised controlled trials (RCTs) that compared chemoprophylaxis of contacts of patients with leprosy against no intervention, placebo or other chemoprophylaxis schemes were eligible for inclusion; studies where the intervention group included vaccines were excluded. The main outcome was diagnosis of leprosy (secondary cases) in contacts of patients with the disease (primary cases).

All of the included studies were conducted in highly endemic populations in Asia (mostly India) and included both adults and children. Treatments, at varying doses and durations, included acedapsone, dapsone, rifampicin, ofloxacin and minocycline; the comparator for all studies was placebo. Most studies applied clinical criteria for leprosy diagnosis; positive bacilloscopy in slit skin smears was also used. Most RCTs included close contacts of leprosy patients or both household and community contacts. The type of disease in the primary case (paucibacillary and multibacillary leprosy) was reported in less than a third of studies.

Two independent reviewers selected studies for inclusion in the review; disagreements were resolved by referral to a third author.

Assessment of study quality
Study quality was assessed according to the criteria: sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and other sources of bias. An overall assessment categorised studies as either a low or high risk of bias.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted relevant data to derive relative risk (RR) for dichotomous outcomes and mean differences for continuous outcomes; disagreements were resolved by consensus of all authors. Authors were contacted for additional data.

Methods of synthesis
Pooled relative risks and weighted mean differences (WMD) and their 95% confidence intervals (CI) were calculated using a random-effects model (Mantel-Haenszel). Heterogeneity was assessed using the $I^2$ tests (high levels of heterogeneity were defined as $I^2 > 70\%$). Analyses were based on intention-to-treat. Subgroup analyses were undertaken to assess the impact of: specific drugs, diagnostic criteria, gender proportions, age, geographic areas, drug dosages and study quality. Numbers needed to treat (NNT) to prevent one case of leprosy were calculated.

**Results of the review**

Seven RCTs (n=66,311) were included in the review. One RCT had a low risk of bias. Generation and concealment of sequence were reported adequately in two studies. Staff and participant blinding was reported in four studies. Duration of follow-up ranged from least two years to 8.5 years.

Chemoprophylaxis was significantly better than placebo for prevention of secondary cases of leprosy at two and four years of follow-up (RR 0.59, 95% CI 0.50 to 0.70; six studies). Compared with placebo, single-dose rifampicin (RR 0.43, 95% CI 0.28 to 0.67; one study, NNT 285), dapsone once or twice weekly for at least two years (RR 0.60, 95% CI 0.48 to 0.76; three studies) and acedapsone every 10 weeks for seven months (RR 0.49, 95% CI 0.33 to 0.72; two studies) were significantly superior in prevention of secondary cases of leprosy. Heterogeneity was absent from all comparisons.

**Authors' conclusions**

Chemoprophylaxis was effective in lowering the incidence of leprosy in contacts of patients diagnosed with the disease.

**CRD commentary**

The review addressed a clear question and was supported by appropriate inclusion criteria. A range of relevant sources were searched and appropriate attempts were made to locate unpublished studies; it was unclear whether language restrictions were applied and so language bias may have been present. Study selection and data extraction were performed in duplicate, which reduced risks of error and bias in the review; it was unclear whether this extended to the assessment of study quality. An appropriate assessment of the quality of the included studies was undertaken; only one study had a low risk of bias. The synthesis using meta-analysis appeared appropriate and an assessment of heterogeneity was undertaken. Subgroup analyses were conducted in an attempt to investigate any possible sources of heterogeneity. This was a well-conducted review and despite the small number of trials of limited quality, the findings reflected the evidence presented and are likely to be reliable. The generalisability of the findings to less endemic populations was unclear.

**Implications of the review for practice and research**

**Practice:** The authors stated that chemoprophylaxis with 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.

**Research:** The authors stated that RCTs that assessed the efficacy and safety of rifampicin in periodic doses to high-risk populations were required; these studies should also undertake subgroup analyses by age, type of contact and type of initial disease. The effect of chemoprophylaxis comparing contacts of multibacillary and paucibacillary forms of leprosy and adjusted estimates for distance between contacts should also be assessed by RCTs.

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