Chemoprophylaxis is effective in the prevention of leprosy in endemic countries: a systematic review and meta-analysis

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Authors' objectives
To quantify the efficacy of chemoprophylaxis in the prevention of leprosy.

Searching
MEDLINE, EMBASE and reference lists were searched, although the search dates and search terms were not reported. The authors of unpublished trials were contacted.

Study selection
Study designs of evaluations included in the review
Published studies of any design were included, such as placebo-controlled RCTs, non-randomised controlled trials, and uncontrolled mass intervention trials. The majority of the RCTs were double-blind.

Specific interventions included in the review
Studies were included if they assessed chemoprophylaxis in the prevention of leprosy. The drugs included were oral dapsone, intramuscular acedapsone and, in one study, rifampicin. The drugs were taken in various doses according to both the age of the participants and the study.

Participants included in the review
The majority of the studies were of schoolchildren, although some included young people up to the age of 25 years. Most studies were of those in close contact with leprosy cases, frequently household contacts. One randomised controlled trial (RCT) included all the healthy young people in 54 villages. The uncontrolled studies were of whole communities. The majority of the trials were carried out in India, with others in Korea, Uganda and the Philippines, and one in Polynesia (the rifampicin trial.)

Outcomes assessed in the review
The outcome assessed was the incidence of leprosy amongst participants during the follow-up periods, which were of 2 to 9 years.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Trial design was evaluated and the trials were critically appraised. It was stated that trials were excluded on the basis of limitations in study design or insufficient information, but the criteria used to assess validity were not stated. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following data were extracted: study design; the duration of the trial; the number in each treatment group; drug dosage; the disease incidence rate in each group; and the participants' characteristics in terms of age range and type of contact.
Methods of synthesis
How were the studies combined?
The relative risks (RRs) of the following were combined using a random-effects model: RCTs of dapsone or acedapsone; non-randomised controlled trials of dapsone or acedapsone; and both study designs together.

How were differences between studies investigated?
Chi-squared tests for heterogeneity were carried out.

Results of the review
Fourteen trials were included: 6 RCTs (n=30,395), 6 non-randomised controlled trials (n=7,988), and 2 uncontrolled observational studies (n=4,351).

The RR and the number-needed-to-treat (NNT) were calculated for each controlled trial. The percentage rate of efficacy (i.e. one minus the RR, expressed as a percentage) was also calculated.

The chi-squared tests for heterogeneity indicated there was significant heterogeneity overall and for each study design subgroup. (p-values not given.) This was discussed with reference to the degree of contact of the participants. However, the pooled RRs were still calculated.

The overall pooled RR for both acedapsone and dapsone was 0.40 (95% confidence interval, CI: 0.29, 0.55). This corresponded to a 60% rate of efficacy. The RR was 0.46 (95% CI: 0.32, 0.66) for the pooled RCTs and 0.28 (95% CI: 0.13, 0.59) for the pooled non-randomised controlled trials.

The NNT ranged from 9 to 63 in trials of household contacts (range: 15 to 27 in RCTs), and from 120 to 393 in trials of communities. Acedapsone produced similar results to dapsone; the NNT for acedapsone ranged from 17 to 25. The NNT was higher in the community than in households because a higher infection rate is expected in households.

Only one study of rifampicin was included in the review. This was an uncontrolled study with only an historical incidence rate for comparison, so it was not included in the meta-analysis. It initially found an 80% efficacy rate, which was later revised to 40 to 50%. The uncontrolled trial of acedapsone was described in some detail and showed some success, but the authors concluded that the uncontrolled trials were difficult to interpret and added little to the evidence.

Cost information
Yes. The cost-effectiveness was estimated by calculating the NNT for different categories of participants. However, no costs were reported.

Authors’ conclusions
The evidence showed that chemoprophylaxis against leprosy is an effective way to reduce the incidence of leprosy, particularly in household contacts. The role of chemoprophylaxis needs to be re-examined using newer drugs, given the continuing case-detection rates globally.

CRD commentary
This review addressed a clearly-defined question and appeared to employ an adequate search strategy. However, details of the strategy were not reported, so it is not possible to assess it. The validity criteria were not given. In addition, details of the processes used to select and assess the studies, and extract the data, were not stated. The individual studies were well-described so that important differences could be considered.

In relation to the data analysis, the CIs were quoted but no p-values were given. It is questionable whether the results should have been pooled, given the heterogeneity. An analysis excluding community-based studies would have been appropriate, to complement the NNT results quoted for the RCTs of household contact. No consideration was given to the possibility of dose response, although there were probably too few trials to draw any firm conclusions on dosage.
Although the quoted pooled result of 60% may be an overestimate for household contacts, the review does provide good evidence for a substantial effect of chemoprophylaxis in this group. In addition, the NNT provides the basis for estimating cost-benefits of the treatment.

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

Practice: The authors state that the prevention of leprosy is still relevant in spite of improved treatments, and the review provides evidence that chemoprophylaxis using dapsone or acedapsone is effective.

Research: The authors state that the role of chemoprophylaxis needs to be re-examined using the newer combined chemotherapy drugs that are currently under trial, which could be used to combat infection within households.

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