

# Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial

F Johannes Moet,<sup>1</sup> David Pahan,<sup>2</sup> Linda Oskam,<sup>3</sup> Jan H Richardus,<sup>1</sup> for the COLEP Study Group

## EDITORIAL by Smith

<sup>1</sup>Department of Public Health, Erasmus MC, University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, Netherlands

<sup>2</sup>Rural Health Program, Leprosy Mission Bangladesh, Nilphamari, Bangladesh

<sup>3</sup>Royal Tropical Institute, KIT Biomedical Research, Amsterdam, Netherlands

Correspondence to: J H Richardus  
j.richardus@erasmusmc.nl

BMJ 2008;336:761-4  
doi:10.1136/bmj.39500.885752.BE

## ABSTRACT

**Objective** To determine the effectiveness of chemoprophylaxis using a single dose of rifampicin to prevent leprosy in close contacts.

**Design** Single centre, double blind, cluster randomised, placebo controlled trial.

**Setting** Leprosy control programme in two districts of northwest Bangladesh with a population of more than four million.

**Participants** 28 092 close contacts of 1037 patients with newly diagnosed leprosy. 21 711 contacts fulfilled the study requirements.

**Interventions** A single dose of rifampicin or placebo given to close contacts in the second month of starting the index patient's treatment, with follow-up for four years.

**Main outcome measure** Development of clinical leprosy.

**Results** 18 869 of the 21 711 contacts (86.9%) were followed-up at four years. Ninety one of 9452 contacts in the placebo group and 59 of 9417 in the rifampicin group had developed leprosy. The overall reduction in incidence of leprosy using a single dose of rifampicin in the first two years was 57% (95% confidence interval 33% to 72%).

The groups did not differ between two and four years. The overall number needed to treat (NNT) to prevent a single case of leprosy among contacts was 297 (95% confidence interval 176 to 537). Differences were found between subgroups at two years, both in reduction of incidence and in NNT.

**Conclusion** A single dose of rifampicin given to contacts of patients with newly diagnosed leprosy is effective at preventing the development of clinical leprosy at two years. The effect was maintained, but no difference was seen between the placebo and rifampicin groups beyond two years.

**Trial registration** Current Controlled Trials  
ISRCTN61223447.

## INTRODUCTION

Close contacts of patients with leprosy have an increased risk of contracting the disease.<sup>1</sup> The risk of a contact developing clinical leprosy is related to the physical and genetic distance to the index patient, the age of the contact, and the classification of the index patient's disease.<sup>2</sup>

In the early 1980s dapsone, the treatment of choice for leprosy, was replaced by multidrug therapy—a combination of dapsone, clofazimine, and rifampicin. Before multidrug therapy became the standard treatment for leprosy, randomised controlled trials using

dapsone or acedapsone investigated whether these drugs could prevent leprosy among contacts.<sup>3,4</sup> A meta-analysis of the studies on chemoprophylaxis with prolonged administration of these drugs estimated an overall efficacy of about 60%.<sup>5</sup> Because of disadvantages with dapsone, rifampicin was chosen because of its strong bactericidal effect against *Mycobacterium leprae*, the micro-organism causing leprosy. It was expected to have at least a similar prophylactic effect to dapsone but with fewer doses and shorter duration of administration. A protective efficacy of 40-50% with rifampicin was reported in an uncontrolled trial.<sup>6,7</sup>

The prospective (sero-) epidemiological study on contact transmission and chemoprophylaxis in leprosy (COLEP) trial, started in northwest Bangladesh in 2002, used a single dose of rifampicin as chemoprophylaxis. The methodology of this trial and the analysis of the intake data have been reported.<sup>2,8</sup> We present the results of the analysis after two and four years of follow-up.

## METHODS

The COLEP study was carried out in two districts of northwest Bangladesh, with a population of more than four million people. The study population consisted of close contacts of 1037 patients with newly diagnosed leprosy (see definition on bmj.com).

We grouped patients with negative skin smear results for acid-fast bacilli at all sites and who had no more than five skin lesions as having paucibacillary leprosy, and those with positive smear results at any site or more than five skin lesions as having multibacillary leprosy. Within the paucibacillary group we classified those with only one lesion as having single lesion paucibacillary disease—as this disease is the commonest form of leprosy in this area and because we preferred to include a sufficient number of patients in all categories we limited the number of patients with single lesion disease to 400. After reclassification of 11 on the basis of skin smear results at intake or clinical symptoms, 389 patients had single lesion paucibacillary disease. Three hundred and fifty three patients had paucibacillary leprosy with two to five lesions and 295 had multibacillary leprosy.

The intake of contacts was from June 2002 to the end of December 2003. We categorised contacts according to their physical and genetic distance to the index patient. For physical distance we defined six categories: shares a house and kitchen, shares a kitchen only, shares a house

This article is an abridged version of a paper that was published on bmj.com on 10 March 2008. Cite this article as: BMJ 10 March 2008, doi: 10.1136/bmj.39500.885752.BE

but not kitchen, next door neighbours, neighbours of the neighbours, and social contacts (see [bmj.com](http://bmj.com)).

As only a small proportion of the social contacts satisfied the criteria and most were in fact neighbours of the contacts classed as neighbours of the neighbours, we pooled these two groups in the analysis. The number of contacts sharing a house but not a kitchen was small and therefore we pooled these with contacts who were next door neighbours. For genetic distance we defined two groups—closely related (parent, child, or sibling) and not closely related (all others). Contacts could only be included in the contact group of one patient. We formed subgroups of contacts according to their contact status, age, genetic relation to the index patient, sex, disease classification of the index patient, presence of a BCG scar, and serological status.

We tested blood samples from index cases during intake and from contacts during intake and follow-up for antibodies to *M leprae*-specific phenolic glycolipid-I, using an enzyme linked immunosorbent assay (ELISA) according to established procedures.<sup>9</sup>

Our objective was to determine the effectiveness of chemoprophylaxis using a single dose of rifampicin to prevent leprosy in close contacts. The primary outcome was the development of clinical leprosy.

At intake (after the index patient had received the second dose of multidrug therapy) all contacts of one patient received treatment with either one or more capsules of 150 mg rifampicin or identical placebo capsules without an active (antibiotic) ingredient (see [bmj.com](http://bmj.com) for dosage schedule). Randomisation was at contact group (cluster) level. The participants, field and hospital staff, and primary researchers were blinded to treatment groups (see [bmj.com](http://bmj.com) for details of blinding).

#### Follow-up

The first follow-up started two years after intake, in June 2004, and was completed in February 2006; the second started four years after intake, in June 2006, and was completed at the end of October 2007. The follow-

ups followed the sequence of recruitment to achieve a uniform follow-up period of 48 months. We recorded the registration dates of any diagnosis of leprosy.

#### Statistical analysis

We initially planned analyses at two and four years. If there had been no effect at two years we could have discontinued the trial. This was firstly because an effect beginning after two years was unlikely, and secondly because an overwhelming effect would call for earlier recommendations for implementation of the intervention in routine leprosy control. This meant that, for the sake of blinding, analyses such as a survival analysis could not be done after the first follow-up period. The power calculations were based on the total follow-up period of four years.

Statistical analyses were done using SAS software, version 9.1. We used techniques for the analysis of survey samples to account for the clustering at the level of the index patient. Bivariate associations were investigated using “proc surveyfreq” and the Rao Scott  $\chi^2$ . Also we used “proc surveylogistic” instead of the ordinary logistic regression procedure. We report odds ratios, but because of the low prevalence of the outcome these are comparable with relative risks. The number needed to treat (NNT) was calculated per subgroup of contacts. A significance level of 5% was used in all tests. We converted the probabilities of having developed leprosy during the follow-up period of two years to incidence rates at one year assuming a constant hazard during the period. To obtain confidence intervals we applied standard errors for the probability around the log (rate).

#### RESULTS

Overall, 28 092 eligible contacts were identified (see [bmj.com](http://bmj.com)). After exclusions (see [bmj.com](http://bmj.com)) 21 711 contacts were included in the trial. The groups were well balanced (see [bmj.com](http://bmj.com)).

Cases of leprosy in contacts of patients with newly diagnosed leprosy by treatment during four years' follow-up, with incidence rates per 10 000 person years at risk

Treatment	Leprosy			Total	No leprosy	Total investigated	Incidence rate per 10 000 person years at risk (95% CI)
	Single lesion paucibacillary	Paucibacillary with 2-5 lesions	Multibacillary				
<b>Placebo</b>							
Follow-up (years):							
1-2	28	30	9	67	9939	10 006	33.59 (26.42 to 42.72)
3-4	8	11	5	24	9361	9385	12.80 (8.58 to 19.11)
1-4	36	41	14	91	—	—	
<b>Rifampicin</b>							
Follow-up (years):							
1-2	15	10	4	29	9922	9951	14.59 (10.14 to 21.01)
3-4	16	8	6	30	9358	9388	16.00 (11.18 to 22.90)
1-4	31	18	10	59	—	—	

Overall reduction in incidence in rifampicin group:

During years 1-2, 56.5% (95% confidence interval 32.9% to 71.9%); Rao Scott  $\chi^2=13.476$  (df=1), P=0.0002; overall number needed to treat 265 (95% confidence interval 176 to 537). During years 1-4, 34.9% (9.8% to 53.0%); Rao Scott  $\chi^2=5.4019$  (df=1), P=0.02; overall number needed to treat 297 (170 to 1206).

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Chemoprophylaxis with prolonged administration of dapsone had an overall efficacy in preventing leprosy in contacts of about 60%

Two doses of rifampicin had a protective efficacy of 40-50% in an uncontrolled trial

**WHAT THIS STUDY ADDS**

A single dose of rifampicin in contacts of new patients with leprosy was 57% effective at preventing the development of leprosy after two years

No further effect was found between two and four years

Of the 21 711 contacts, 20 032 (92.3%) were seen during the first follow-up (years 1 to 2) and 18 869 (86.9%) during the second follow-up (years 3 to 4). Among these, 96 new patients with leprosy were found during the first follow-up and another 54 during the second follow-up (table). Over the four years of observation 91 participants developed leprosy in the placebo group and 59 in the rifampicin group. The reduction in incidence in the rifampicin group was 56.5% (95% confidence interval 32.9% to 71.9%;  $P=0.0002$ ) in the first two years and 34.9% (9.8% to 53.0%;  $P=0.02$ ) during the four years. The great reduction of new cases in the rifampicin group occurred in the two years after treatment; in years 3 and 4 no statistically significant difference was found between the number of new leprosy cases in the groups, although the number was slightly higher in the rifampicin group (30 *v* 24). The overall NNT to prevent one new case of leprosy was 265 (95% confidence interval 176 to 537) after two years and 297 (170 to 1206) after four years.

**DISCUSSION**

The overall incidence of leprosy among contacts of patients with newly diagnosed disease can be reduced by a single dose of rifampicin. A reduction of 57% was achieved in the two years after treatment but no statistically significant difference was observed between the rifampicin and placebo groups in years 3 and 4 after treatment.

The strength of the trial is its robust design and the large number of participants who could be included fairly quickly because of the relatively high incidence of leprosy in the study area. Although we see no reason to assume otherwise we cannot be certain that the results apply to situations where leprosy is less highly endemic.

The results of our study confirm those of previous studies on the efficacy of rifampicin prophylaxis. It seems, however, that this effect is not the same for all subgroups of contacts. Contacts who were not closely related to the index patient or lived further away, and who on the basis of the intake data were expected to be at a lower risk,<sup>2</sup> benefited more from prophylaxis. This inverse relation between efficacy and expected risk also seems to exist for classification of disease in the index patient. By contrast, a direct relation with age of the

contact is suggested, higher efficacy being recorded in those groups with a higher incidence of leprosy.

Prophylaxis seemed more effective in females and in those contacts who were seronegative for antibodies to *M leprae* specific phenolic glycolipid-I at intake. Research has indicated, however, that contacts who are seropositive for such antibodies are at an increased risk of developing leprosy, especially multibacillary disease.<sup>10</sup>

The incidence rate of new cases of leprosy in the placebo group between two and four years showed a downward trend, whereas the rate remained similar in the rifampicin group over the two observation periods (see table). This downward trend can be understood as regular surveys of contacts with treatment of newly detected cases is in itself an intervention by removing potential sources of infection and thereby reduced transmission to contacts. The difference between the groups is determined primarily by a reduction of paucibacillary leprosy in the rifampicin group in the first two years. After four years we cannot yet establish to what extent there is a true prevention of new cases of leprosy by intervention with rifampicin. There may be merely a delay in the occurrence of disease, which can only be confirmed through longer observation.

The findings of our trial are consistent with those of a study from Indonesia.<sup>11</sup> That study found no effect of rifampicin in communities where only household contacts and direct neighbours were given prophylaxis, but showed a significant effect in those communities where everybody was given prophylaxis. But even in those communities, rifampicin prophylaxis seemed to be more effective in non-contacts than in household contacts. A possible explanation could be that by the time the prophylaxis is given the potential bacillary load in close (physical and genetic) contacts, seropositive contacts, and contacts of patients with multibacillary disease is on average already too high to be eliminated by a single (double in Indonesia) dose of rifampicin. This possibly higher average bacterial load could be caused by either a higher exposure or a higher vulnerability.

In summary, a single dose of rifampicin given to contacts of new patients with leprosy was 57% effective in preventing the development of clinical leprosy after two years but a further effect could not be shown between two and four years. The finding of single dose rifampicin as a cheap and practical preventive intervention for contacts of patients with leprosy is promising.

We thank the staff of the leprosy control unit and the statistical department of the Rural Health Program (formerly Danish Bangladesh Leprosy Mission) in Nilphamari and Rangpur for their dedicated work, often under difficult conditions.

**Contributors:** See bmj.com.

**Funding:** American Leprosy Missions and the Leprosy Mission International.

**Competing interests:** None declared.

**Ethical approval:** This study was approved by the ethical review committee of the Bangladesh Medical Research Council in Dhaka (BMRC/ERC/2001-2004/799).

The COLEP Study Group consists of Wim H van Brakel, Paul R Klatscher, Paul R Saunderson, W Cairns S Smith, Steve G Withington (scientific advisors), F Johannes Moet, Linda Oskam, David Pahan, Jan Hendrik Richardus (project director), Ron P Schuring, Roel Faber, and Gerard J J M Borsboom. **Provenance and peer review:** Not commissioned; externally peer reviewed.

- 1 Doull JA, Guinto RS, Rodriguez JN, Bancroft H. The incidence of leprosy in Cordova and Talisay, Cebu, Philippines. *Int J Lepr* 1942;10:107-31.
- 2 Moet FJ, Pahan D, Schuring RP, Oskam L, Richardus JH. Physical distance, genetic relationship, age, and leprosy classification are independent risk factors for leprosy in contacts of patients with leprosy. *J Infect Dis* 2006;193:346-53.
- 3 Noordeen SK, Neelan PN. Chemoprophylaxis among contacts of non-lepromatous leprosy. *Lepr India* 1976;48(4 suppl):635-42.
- 4 Noordeen SK. Long term effects of chemoprophylaxis among contacts of lepromatous cases. Results of 8 1/2 years follow-up. *Lepr India* 1977;49:504-9.
- 5 Smith CM, Smith WC. Chemoprophylaxis is effective in the prevention of leprosy in endemic countries: a systematic review and meta-analysis. MILEP2 Study Group. *Mucosal immunology of leprosy. J Infect* 2000;41:137-42.

- 6 Cartel JL, Chanteau S, Boutin JP, Taylor R, Plichart R, Roux J, et al. Implementation of chemoprophylaxis of leprosy in the Southern Marquesas with a single dose of 25 mg per kg rifampin. *Int J Lepr Other Mycobact Dis* 1989;57(4):810-6.
- 7 Cartel JL, Chanteau S, Moulija-Pelat JP, Plichart R, Glaziou P, Boutin JP, et al. Chemoprophylaxis of leprosy with a single dose of 25 mg per kg rifampin in the southern Marquesas; results after four years. *Int J Lepr Other Mycobact Dis* 1992;60:416-20.
- 8 Moet FJ, Oskam L, Faber R, Pahan D, Richardus JH. A study on transmission and a trial of chemoprophylaxis in contacts of leprosy patients: design, methodology and recruitment findings of COLEP. *Lepr Rev* 2004;75:376-88.
- 9 Bührer-Sékula S, Samo EN, Oskam L, Koop S, Wichers I, Nery JA, et al. Use of ML dipstick as a tool to classify leprosy patients. *Int J Lepr Other Mycobact Dis* 2000;68:456-63.
- 10 Oskam L, Slim E, Bührer-Sekula S. Serology: recent developments, strengths, limitations and prospects: a state of the art overview. *Lepr Rev* 2003;74:196-205.
- 11 Bakker MI, Hatta M, Kwenang A, Van Benthem BH, Van Beers SM, Klatscher PR, et al. Prevention of leprosy using rifampicin as chemoprophylaxis. *Am J Trop Med Hyg* 2005;72:443-8.

Accepted: 13 February 2008

## Getting to the bottom of evidence based medicine

“Which way up should I put the suppository?” I’ve asked this question of countless junior obstetricians over the years as we administer rectal analgesia after a caesarean section.<sup>1</sup> Despite thinking it might be a trick question, they all want to insert the pointed end of the bullet shaped object first.<sup>2</sup> Surely that’s how they are designed, and it would be more comfortable?

Well, no. It was Minerva herself who drew this to my attention: a trial confirms that blunt end first is preferable.<sup>3</sup> Possibly because of the tapered shape and tone of the sphincter, fingers rarely need to be inserted into the anal canal (1% v 83%) as the suppository is “sucked” up and fewer suppositories are expelled (0 v 3%). There is 82% less invasive administration, and drug delivery and costs should improve by 3%. So, here is a simple, easy improvement to your practice. Or is it? At this point, I get an alarmingly familiar stare from the junior (is she right or completely barking?). “I don’t wish to practise authority based medicine,” I say, “If you don’t believe me, please check on Medline.” But only one has.

Good doctors, rightly, are risk averse and conservative. As individuals, we find change difficult. What is fascinating about the discourse of evidence based medicine is the psychological challenge it presents—of changing one’s practice from less effective to more effective. Changing on the basis of new evidence means accepting the uncomfortable notion that we did it wrong, or less well, before. Thus we have needlessly harmed people in the past. This is painful for health professionals, motivated by the urge to help and heal, even if our actions were unintentional or the evidence didn’t exist previously. Some find it easy to say “Well, better stop harming now than carry on,” but denial is simpler, powerful, and comforting.

Which brings us back to the humble suppository as an excellent educational tool. The correct answer about mode of insertion is counterintuitive, the past harms are unpleasant (but relatively minor—not dead or damaged patients), and the lesson applies to nearly all NHS clinicians. Having failed to get a directorate-wide

suppository guideline agreed, I decided to opt for a hospital-wide protocol. The chief pharmacist examined, and accepted, the arguments. We should indeed be inserting suppositories the other way, base first. The only problem was that all suppository packs contain the traditional, incorrect instruction, which would confuse patients. So, he concluded, it has to be an NHS-wide policy. I have written to the National Institute for Health and Clinical Excellence twice, but have had no reply and not found it on their programme of work. Why not? A 3% saving of the NHS suppository bill could be substantial.

The savings would be greater still if more attention was drawn to cheaper rectal drugs that might be used more frequently. A technique that doesn’t require finger insertion might help patient acceptability. The educational benefits of applying evidence based medicine for every doctor, nurse, midwife, health visitor, and patient in the UK would be phenomenal.<sup>4</sup> A problem remains in persuading the drug companies to change the patient information leaflets and potentially lose 3% profits.

In the meantime, don’t let the multinational, global political issues stop you reflecting on and changing your practice.

Susan Bewley consultant obstetrician,  
Guys and St Thomas’ Foundation Trust, London  
susan.bewley@gstt.nhs.uk

- 1 Lim NL, Lo WK, Chong JL, Pan AX. Single dose diclofenac suppository reduces post-caesarean PCEA requirements. *Can J Anaesth* 2001;48:383-6
- 2 Moppett S, Parker M. Insertion of a suppository. *Nurs Times* 1999;95(suppl 1-2).
- 3 Abd-el-Maeboud KH, el-Naggar T, el-Hawi EM, Mahmoud SA, Abd-el-Hay S. Rectal suppository: common sense and mode of insertion. *Lancet* 1991;338:798-800.
- 4 Bradshaw A, Price L. Rectal suppository insertion: the reliability of the evidence as a basis for nursing practice. *J Clin Nurs* 2007;16:98-103.