Chemoprophylaxis in the prevention of leprosy

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**Risk groups**

Close contacts of leprosy patients have a higher risk to develop leprosy (COLEP) and are an appropriate group for targeted interventions.

Trials in Indonesia and Bangladesh

**Hypothesis:**
- Leprosy can be prevented by chemoprophylaxis

**Overall aim of the studies:**
- To find effective tools for prevention of leprosy that can be applied by routine leprosy control programmes under field circumstances
Study 1: Indonesia

**Partners:** KIT Biomedical Research (Amsterdam, Netherlands) & Hasanuddin University (Makassar, Indonesia)

**Total duration of study:** 7 years (2000-2006)

**Study area:** 5 small, isolated islands in the Flores Sea, Indonesia

### Study design

**2000:**
- Active population screening of leprosy
- Treatment of new patients with MDT
- Supply prophylactic treatment to contacts in July **AND** November

**2001-2006:**
- Yearly active screening of population
- Treatment of new patients with MDT
Prophylactic regimens

Compare 2 types of prophylactic regimens:

1. **Contact regimen**: prophylaxis only for contacts (household contacts, direct neighbours and next neighbours)

2. **Blanket regimen**: prophylaxis for all eligible persons

with

3. **Control group**: no prophylaxis

**Limitations:**
- Not randomized
- Not blind
- Not placebo-controlled

Results of annual screening (after 3 years)

<table>
<thead>
<tr>
<th></th>
<th>Cohort in 2000</th>
<th>Cohort after 3 years</th>
<th>% complete follow-up</th>
<th>New patients in cohort</th>
<th>Cum. Incidence after 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1251</td>
<td>818</td>
<td>65.4%</td>
<td>11</td>
<td>0.0110</td>
</tr>
<tr>
<td>Contact</td>
<td>1632</td>
<td>1176</td>
<td>72.1%</td>
<td>15</td>
<td>0.0099</td>
</tr>
<tr>
<td>Blanket</td>
<td>1080</td>
<td>874</td>
<td>80.9%</td>
<td>3</td>
<td>0.0031</td>
</tr>
<tr>
<td>Total</td>
<td>3963</td>
<td>2868</td>
<td>72.4%</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

1. Cumulative incidence of blanket group significantly lower compared to control group (p=0.03)
2. Effectiveness of blanket treatment: 74.6% (95% CI: 5.4-93.2)
3. No difference between contact and control groups
Cumulative incidence over time per group (3 years)

Cumulative incidence over time per group (6 years)

Evaluation after 3 years
Conclusions Indonesia study

1. Population-based prophylaxis was associated with a reduced leprosy incidence in the first 3 years after implementation.

2. 6 years after implementation this difference was not statistically significant anymore.

- Longer follow-up of the cohort will tell us more about the effect of yearly screening and the longer term effect.

Study 2: Bangladesh (COLEP)

Partners: Erasmus MC, Rotterdam (NL), The Leprosy Mission Bangladesh, KIT Biomedical Research, Amsterdam (NL)

Total duration of study: 6 years (2001-2007)

Study area: Two districts in northwest Bangladesh

- Nilphamari & Rangpur districts
- Population ± 4 million
- 1,500 - 1,800 new cases/year
Study design COLEP

Trial group
(20,000 contacts from 1,000 new leprosy patients)

500 groups rifampicin
n = 10,000

500 groups placebo
n = 10,000

How many new cases of leprosy after 2 and 4 years?

Single-centre, cluster randomised, double blind, placebo-controlled trial

Prophylactic regimen

Treatment schedule:
- 1 dose of placebo or rifampicin (300-600 mg based on age and weight)
- 6 weeks after start of MDT treatment index patient

Treatment allocation:
- Placebo: 10,854 (520 contact groups)
- Rifampicin: 10,857 (517 contact groups)

- Follow-up after 2 years: 92%
- Follow-up after 4 years: 87%
### Results years 1 and 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-up during</th>
<th>Leprosy</th>
<th>No leprosy</th>
<th>Risk per 10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLPB</td>
<td>PB2-5</td>
<td>MB</td>
<td>Total</td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall reduction in rifampicin group: **56.5%**  
(95% CI = 32.9-71.9); p = 0.0002

Overall number needed to treat: **265**  
(95% CI = 176-537)

### Results years 3 and 4

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-up during</th>
<th>Leprosy</th>
<th>No leprosy</th>
<th>Risk per 10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLPB</td>
<td>PB2-5</td>
<td>MB</td>
<td>Total</td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results years 1 to 4

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-up during</th>
<th>Leprosy</th>
<th>No leprosy</th>
<th>Total</th>
<th>Risk per 10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLPB/PB2/MB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Years 1-2</td>
<td>28</td>
<td>30</td>
<td>9</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Years 3-4</td>
<td>8</td>
<td>11</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Years 1-4</td>
<td>36</td>
<td>41</td>
<td>14</td>
<td>91</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Years 1-2</td>
<td>15</td>
<td>10</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Years 3-4</td>
<td>16</td>
<td>8</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Years 1-4</td>
<td>31</td>
<td>18</td>
<td>10</td>
<td>59</td>
</tr>
</tbody>
</table>

Overall reduction in rifampicin group: 34.9% (95% CI = 9.8-53.0); p = 0.02
Overall number needed to treat: 297 (95% CI = 170-1206)

Incidence (per 10,000) at 2 and 4 years
Effect of rifampicin by risk group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Rifampicin</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closely related</td>
<td>18/1585</td>
<td>13/1507</td>
<td>0.76</td>
<td>0.49</td>
</tr>
<tr>
<td>Not closely related</td>
<td>49/8386</td>
<td>16/8458</td>
<td>0.32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Index patient MB</td>
<td>21/2846</td>
<td>10/2628</td>
<td>0.52</td>
<td>0.12</td>
</tr>
<tr>
<td>Index patient PB2-5</td>
<td>22/3133</td>
<td>9/3408</td>
<td>0.38</td>
<td>0.022</td>
</tr>
<tr>
<td>Index patient PB1</td>
<td>24/3992</td>
<td>10/3931</td>
<td>0.42</td>
<td>0.023</td>
</tr>
<tr>
<td>Household contact</td>
<td>13/912</td>
<td>6/924</td>
<td>0.46</td>
<td>0.17</td>
</tr>
<tr>
<td>Neighbour 1</td>
<td>17/2770</td>
<td>8/2544</td>
<td>0.51</td>
<td>0.12</td>
</tr>
<tr>
<td>Neighbour 2</td>
<td>32/5559</td>
<td>8/5792</td>
<td>0.24</td>
<td>0.0003</td>
</tr>
<tr>
<td>BCG scar</td>
<td>15/4023</td>
<td>7/3962</td>
<td>0.47</td>
<td>0.13</td>
</tr>
<tr>
<td>No BCG scar</td>
<td>52/5878</td>
<td>22/5917</td>
<td>0.42</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

Effect of rifampicin seems to be highest in contact groups with lowest a priori risk

Conclusions COLEP study

- Rifampicin chemoprophylaxis reduces the incidence of leprosy
- The effect was maintained, but no difference between the placebo and treatment groups were seen beyond two years
- The effect is highest in the lowest a priori risk groups (contacts further removed from patient, both genetically and physically)
- Regular contact surveys with treatment of newly found cases is an effective intervention in itself!
Modeling outcomes of household interventions

- To compare the impact at population level of three interventions targeted at **household contacts** of patients
  
  - Chemoprophylaxis
  - BCG vaccination
  - Early diagnosis of sub-clinical infections

  Mathematical modeling (micro-simulation) using the **SIMCOLEP** model

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The **SIMCOLEP** model

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additional interventions
Interventions (at household level)

- Chemoprophylaxis
  - 0.5 cure among contacts developing leprosy

- BCG Vaccination
  - protective effect of 0.5

- Early diagnosis of sub-clinical infections
  - probability of test of 0.7 to detect a sub-clinical case

Preliminary results (new case detection rate over time)
Conclusions

- Chemoprophylaxis and BCG interventions aimed at household contacts only does not have a large impact on the new case detection rate of leprosy in the population.

- For (preventive) interventions such as (BCG) vaccination and chemoprophylaxis to have impact at population level, these should be applied to a larger group of contacts than household contacts only (neighbours, social contacts, total populations?)

- **Early diagnosis (diagnosis of pre-clinical infection) and treatment** is the single important intervention that can be expected to impact on the transmission of *M. leprae* in the population!

Additional research needs

1. Treatment regimens for very high risk groups
2. Effects of prophylaxis beyond neighbour “2” contacts
3. Long-term effects of chemoprophylaxis
4. Development of tools to detect sub-clinical leprosy to study tailor-made prophylactic treatment regimens
5. Further operational / health systems research to identify characteristics of the public health system that are critical for a successful implementation of chemoprophylaxis under routine leprosy control programme conditions
Acknowledgements

The studies in Indonesia and Bangladesh could not have been completed without support of the many dedicated field workers involved.

Funding for the studies has been received by:

- Netherlands Leprosy Relief (study in Indonesia and SIMCOLEP)
- American Leprosy Missions (COLEP)
- The Leprosy Mission International (COLEP)

Thank you!