Effectiveness of Single Dose Rifampicin in Prevention of Leprosy among High Risk Community Contacts


Ministry of Public Health
Thailand
Prevalence rate 1984-1994

PR/10,000

1984: 8.87
1985: 7.99
1986: 6.46
1987: 5.37
1988: 4.1
1989: 3
1990: 2.16
1991: 1.44
1992: 1.2
1993: 1.06
1994: 0.84
Number of New Cases and Detection rate 1994-2002

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
<th>DR/100,000 pop.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>1161</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>1297</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>1197</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>1457</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>1111</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>864</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>1037</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>797</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>1000</td>
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</tbody>
</table>
Rationale

• Protective approaches
  • Immunoprophylaxis
  • Chemoprophylaxis
Prophylactic Regimens

- Rifampicin
  - Single dose 600 mg
  - Efficacy, safe and cost effective
  - Rifampicin resistant mutants – Negligible
- ROM
  - Efficacy ~ Rifampicin, more side effects, more expensive
- Rifapentine
  - not commercially available
Previous studies with Rifampicin

- In Southern Marquesas Islands 1988
  - Detection rate 48/100,000
  - Target Population: Blanket approach
  - Rifampicin 25 mg/kg single dose
  - Methodology
    - experimental study with historical control
  - Follow up 10 yrs
  - Efficacy: 35-40%
Previous studies with Rifampicin

• India 1999
  • High endemic situation
  • Target populations: household contacts
  • Rifampicin 10 mg / kg single dose
  • Randomized, double blind and placebo-controlled
  • Follow up 5 years
Rationale for the study

• Prior to 2002, previous studies had been:
  • Uncontrolled trials
  • Unblinded studies
  • Thailand had a different leprosy situation, low prevalence situation
  • Different target contact group

• Therefore, new research with **better study design** was needed
  • to find out the effectiveness of chemoprophylaxis
  • in **specific contact groups**
Objectives

To compare effectiveness between rifampicin and placebo as chemoprophylaxis for leprosy among high risk community contacts at 5 years follow up
Research Methodology
Study design

• Randomized Controlled Trial

Population

• Target Population
  • High risk community contacts
  • in the North Eastern region of Thailand
Inclusion criteria

High risk community contacts

Household contacts

- Shared the same house for at least 1 month, before treatment

Neighboring contacts:

- within 20 meters surrounding the house of index cases
- at least 1 month.

Social contacts

- social activities with index cases
- at least 3 hours/day and 3 days/week for at least 1 month.
Definition of Index case

• **MB cases** in high risk area

• High risk area
  • District with
    • Prevalence rate > 1:10,000
    • Continuing New case reports for 5 consecutive years
    • or cases in children > 5%
Sample size Calculation

Effect size = 50% reduction of incidence
P1 = 0.04  \quad P2 = 0.02
Alpha-level = 0.05, two tailed test
Power of the test 80%

\[ n = \frac{Z_{1-\alpha/2} \sqrt{2P(1-P)}}{Z_{1-\beta} \sqrt{P_1(1-P_1)+P_2(1-P_2)}}^2 \]

\[ P = \frac{P_1+P_2}{2} \]

n = 1138, if drop out 20%, \quad n = 1365 in each arm
Randomisation

- The sampling frame
  - District with PR > 1:10,000

- Cluster randomization
  - Sub-district as randomisation unit
  - The same sub-district, the same regimen

- Random allocation to regimen A or B
Exclusion Criteria

1. Children < 2 years
2. Leprosy cases or treated leprosy cases
3. Tuberculosis/ treated tuberculosis cases/
   Suspected tuberculosis cases
4. Pregnancy
Blinding

- Allocation concealment
- Pharmacist at central office
  - kept randomization running number
  - the code was revealed after data analysis
- Blinding
  - The participants
  - The field researchers
  - The statistician: Data analysis
Variables

• Demographic
  • age, gender
  • Type of Index
  • MB
    • LL, BL, BB, BT
• Antibody to PGL-I of contacts at intake
• Type of Contacts
  • Household, Neighboring, Social
Main Outcome Measurement

• Development of clinical leprosy in 5 years
  • Standard criteria of diagnosis of leprosy
  • Clinical signs and slit skin smear
    • Standardization
    • Inter - observer agreement by Kappa 0.85
    • Assessment consensus from two researchers

• Assessment every year
• Final outcome at the 5th year
Intervention

• 1 month after treatment of index cases
• Regimen B: Rifampicin
  • 600 mg for adult
  • 450 mg for children 5-9 years
  • 150 mg for children 2-4 years
• Regimen A: Placebo
  • Capsule of placebo identical to Rifampicin
  • Same capsule without active ingredient
Data analysis

• Intention-to-treat principle
• Inferential Statistics
  • Chi square
  • Estimation
  • 95% CI of Relative Risk
  • p- value
Results
Duration of the study

• Recruitment
  • Started 2003
    • From 95 index cases.
    • 2,820 met the inclusion criteria
    • After applying exclusion criteria,
      • 2,749 were randomized and enrolled in our study.
  • Completed in 2005
• Follow up
  • Started 2004
  • Finished 2010
Follow Up

• 17% Loss to follow up
• Reasons for loss
  ▪ Relocation 98%
  ▪ Death 0.6%
  ▪ Unknown 1.4%
## Characteristics of contacts enrolled in the study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Placebo percentage</th>
<th>Rifampicin percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-9</td>
<td>196</td>
<td>3.38</td>
<td>3.75</td>
</tr>
<tr>
<td>10-14</td>
<td>205</td>
<td>3.93</td>
<td>3.53</td>
</tr>
<tr>
<td>15-19</td>
<td>104</td>
<td>1.93</td>
<td>1.86</td>
</tr>
<tr>
<td>20-29</td>
<td>238</td>
<td>4.40</td>
<td>4.26</td>
</tr>
<tr>
<td>30-44</td>
<td>833</td>
<td>13.93</td>
<td>16.37</td>
</tr>
<tr>
<td>45-60</td>
<td>813</td>
<td>14.84</td>
<td>14.73</td>
</tr>
<tr>
<td>&gt;60</td>
<td>346</td>
<td>3.93</td>
<td>6.04</td>
</tr>
<tr>
<td>Unknown</td>
<td>14</td>
<td>0.11</td>
<td>0.40</td>
</tr>
<tr>
<td>Total</td>
<td>2,749</td>
<td>1,349 (49.07%)</td>
<td>1,400 (50.93%)</td>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Male</td>
<td>1,133</td>
<td>20.19</td>
<td>21.03</td>
</tr>
<tr>
<td>• Female</td>
<td>1,616</td>
<td>28.88</td>
<td>29.90</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2,749</td>
<td>1,349 (49.07%)</td>
<td>1,400 (50.93%)</td>
</tr>
<tr>
<td><strong>Type of index cases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• LL</td>
<td>517</td>
<td>8.40</td>
<td>10.40</td>
</tr>
<tr>
<td>• BL</td>
<td>910</td>
<td>16.48</td>
<td>16.62</td>
</tr>
<tr>
<td>• BB</td>
<td>222</td>
<td>5.20</td>
<td>3.06</td>
</tr>
<tr>
<td>• BT</td>
<td>1,100</td>
<td>19.17</td>
<td>20.84</td>
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<tr>
<td>Antibody to PGL-1 in contacts at intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1,052(38%)</td>
<td>18.92</td>
<td>19.35</td>
</tr>
<tr>
<td>Positive</td>
<td>1,697(62%)</td>
<td>30.16</td>
<td>31.58</td>
</tr>
<tr>
<td>+1</td>
<td>1244</td>
<td>22.04</td>
<td>23.21</td>
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<tr>
<td>+2</td>
<td>324</td>
<td>6.04</td>
<td>5.75</td>
</tr>
<tr>
<td>+3</td>
<td>109</td>
<td>1.75</td>
<td>2.22</td>
</tr>
<tr>
<td>+4</td>
<td>20</td>
<td>0.33</td>
<td>0.40</td>
</tr>
<tr>
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<th>Rifampicin percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2749(100%)</td>
<td>1349 (49.07%)</td>
<td>1400 (50.93%)</td>
</tr>
<tr>
<td>Type of Contacts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household</td>
<td>8</td>
<td>4.44</td>
<td>3.46</td>
</tr>
<tr>
<td>Neighboring</td>
<td>81</td>
<td>38.96</td>
<td>42.45</td>
</tr>
<tr>
<td>Social</td>
<td>11</td>
<td>5.67</td>
<td>5.02</td>
</tr>
</tbody>
</table>


Final outcome at the 5\textsuperscript{th} years

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>No leprosy</th>
<th>Leprosy</th>
<th>Relative risk</th>
<th>95%CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1,349</td>
<td>1,335</td>
<td>14</td>
<td>0.48</td>
<td>0.18-1.27</td>
<td>0.105</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>1,400</td>
<td>1,393</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2,749</td>
<td>2,728</td>
<td>21</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
## Subgroup analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>placebo</th>
<th>Rifampicin</th>
<th>P-value</th>
<th>Relative risk (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of index case</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,335</td>
<td>14</td>
<td>1,393</td>
<td>7</td>
<td>0.127</td>
<td>0.48(0.18-1.27)</td>
</tr>
<tr>
<td>225</td>
<td>6</td>
<td>284</td>
<td>2</td>
<td>0.148</td>
<td>0.27 (0.04-1.145)</td>
</tr>
<tr>
<td>448</td>
<td>5</td>
<td>456</td>
<td>1</td>
<td>0.122</td>
<td>0.01 (1.72-113.03)</td>
</tr>
<tr>
<td><strong>LL+BL</strong></td>
<td>673</td>
<td>740</td>
<td>3</td>
<td><strong>0.029</strong></td>
<td><strong>0.25 (0.06-0.96)</strong></td>
</tr>
<tr>
<td>138</td>
<td>0</td>
<td>84</td>
<td>0</td>
<td>1.00</td>
<td>1.64 (0.00-215230.74)</td>
</tr>
<tr>
<td><strong>BT</strong></td>
<td>524</td>
<td>569</td>
<td>4</td>
<td>1.00</td>
<td>1.23 (0.23-6.86)</td>
</tr>
</tbody>
</table>
Discussion
Principal Findings

• At the 5th year follow up
• There was no significant difference between the Rifampicin and placebo group
• Among the contacts from MB index
Discussion

- There was trend for the effectiveness of rifampicin
- But due to sample size it was suitable for detecting 50% risk reduction
- This study does not have enough power
  - to prove the statistical significance for a lower than 50% risk reduction
  - a larger sample size is needed
Discussion

Significant Difference in Subgroups

- Contacts of index cases with LL+BL
- Benefit from chemoprophylaxis
- Relative risk = 0.25, p-value = 0.03
- 75% of cases were protected by chemoprophylaxis
Discussion

• When LL-BL index cases who were the only source of transmission were treated.
• The source of transmission was eliminated.
• Due to chemoprophylaxis by rifampicin, the bacterial load in contacts was eliminated.

• In low endemic situation
  • No more source of transmission in the community.
  • Less likely for contacts to be re-infected.
Discussion

Contacts from BT and BB index cases

• No statistical difference of incidence rate between rifampicin and placebo

This findings could result from

1. Sample size of these sub group was insufficient.
2. Rifampicin might not effective in contacts of BT and BB
Discussion

• Low intensity of exposure from BT index

• It was possible that the contacts of BT index who develop leprosy after Chemoprophylaxis were re-infected with out-of-cluster, undetected, untreated LL+BL cases

• This can be tested by a molecular epidemiology study of *M. leprae* which was not possible in this study.
Discussion

- Our findings are similar to those of the COLEP study in Bangladesh
- that in the 3rd year and 4th year
- There were no significant difference between the groups.
- Suggested that the effect of chemoprophylaxis do not last longer than 2 years
Conclusion

• In low endemic situation
• Rifampicin is not effective to prevent occurrence of leprosy among high risk community contacts of the whole range of MB index in 5 years
• Rifampicin is effective in preventing occurrence of leprosy only among contacts of LL-BL MB index in 5 years
Acknowledgement

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Thank You

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