

Erasmus MC
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Chemoprophylaxis: The COLEP study

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Bangladesh, the COLEP study

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

Total duration of study: 8 years (2001-2009)

Study area: Two districts in northwest Bangladesh



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

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Study design

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?

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

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Prophylactic regimen: single dose Rifampicin (SDR)

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%

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Results years 1 and 2

Treatment	Follow-up during	Leprosy				No leprosy	Total	Risk per 10,000
		SLPB	PB2-5	MB	Total			
Placebo	Years 1-2	28	30	9	67	9939	10006	67.0
	Years 3-4	8	11	5	24	9361	9452	25.6
Rifampin	Years 1-2	15	10	4	29	9922	9951	29.1
	Years 3-4	16	8	6	30	9358	9417	31.9

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)

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Results years 3 and 4

Treatment	Follow-up during	Leprosy				No leprosy	Total	Risk per 10,000
		SLPB	PB2-5	MB	Total			
Placebo	Years 1-2	28	30	9	67	9939	10006	67.0
	Years 3-4	8	11	5	24	9361	9452	25.6
Rifampin	Years 1-2	15	10	4	29	9922	9951	29.1
	Years 3-4	16	8	6	30	9358	9417	31.9

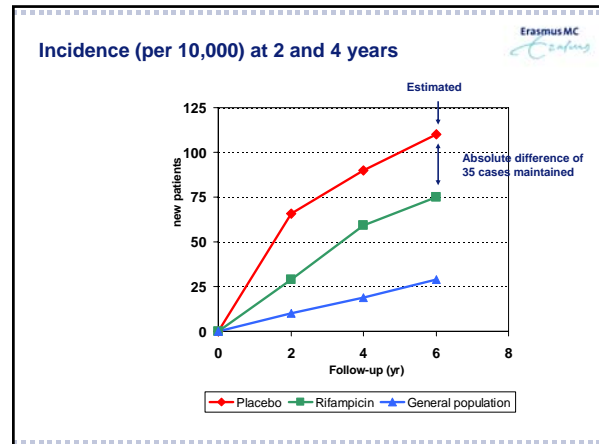
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Results years 1 to 4

Treatment	Follow-up during	Leprosy				No leprosy	Total	Risk per 10,000
		SLPB	PB2-5	MB	Total			
Placebo	Years 1-2	28	30	9	67	9939	10006	67.0
	Years 3-4	8	11	5	24	9361	9452	25.6
	Years 1-4	36	41	14	91			
Rifampin	Years 1-2	15	10	4	29	9922	9951	29.1
	Years 3-4	16	8	6	30	9358	9417	31.9
	Years 1-4	31	18	10	59			

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)



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Effectiveness

- Effect of SDR dependent of **contact level**

Variable	Placebo	Rifampicin	Protective effect	p
Blood related	18/1585	13/1507	24%	0.49
Not blood related	49/8386	16/8458	68%	<0.0001
Index patient MB	21/2846	10/2626	48%	0.12
Index patient PB2-5	22/3133	9/3408	62%	0.022
Index patient PB1	24/3992	10/3931	58%	0.023
Household contact	13/912	6/924	54%	0.17
Neighbour	17/2770	8/2544	49%	0.12
Social	32/5559	8/5792	76%	0.0003

Effect of chemoprophylaxis highest in contact groups with lowest *a priori* risk

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Effectiveness

- Effect of SDR dependent of BCG status

Intervention	Leprosy	No Leprosy	Multivariate*		Protective effect
			OR	95% CI	
None	52	6418	1		
Rifampicin only	22	6462	0.42	0.26-0.70	58%
BCG only	15	4291	0.43	0.25-0.76	57%
Rifampicin and BCG	7	4259	0.20	0.08-0.50	80%

* Adjusted for age, sex, physical distance to and classification of index patient

Effect of chemoprophylaxis with rifampicin is additive to the effect of BCG

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Conclusions COLEP study

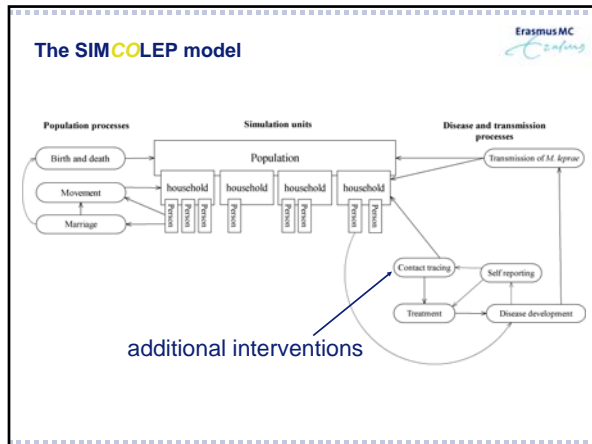
- Rifampicin chemoprophylaxis reduces the incidence of leprosy
- The effect was maintained, but no difference between the placebo and treatment groups was seen beyond two years
- The effect is highest in the lowest *a priori* risk groups (contacts further removed from patient, both genetically and physically)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

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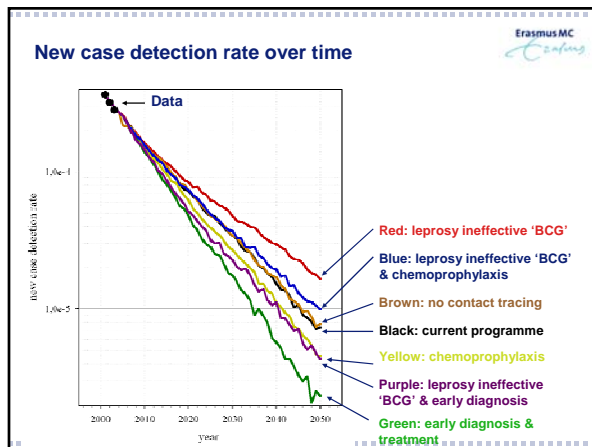
Modeling outcomes of household interventions

- 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



- Interventions (at household level)**
- Assumptions:
- Chemoprophylaxis
 - 0.5 protective effect 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



- Conclusions**
- The current infant BCG vaccination program has a marked effect on the reduction of the leprosy incidence in the population
 - SDR chemoprophylaxis for household contacts gives added reduction of the leprosy incidence in the population
 - Early diagnosis (diagnosis of pre-clinical infection) and treatment can have the largest impact on the leprosy incidence in the population
 - Change to a leprosy non-effective 'BCG' vaccine will be a major set-back for leprosy control, but can be compensated by SDR chemoprophylaxis and early diagnosis

Acknowledgements

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- The Leprosy Mission International (COLEP)

Thank you!

Strategies



2. Population approach:

- Blanket treatment of whole population in a defined geographic area (e.g. sub-district, village, island)
- Comparable to *lymphatic filariasis* (mass chemoprophylaxis)

Strategies: population approach



Advantages:

- Very effective (*Indonesia island study: 75% after 3 years*)
- Impact on *M. leprae* transmission in population
- Cost saving
- Acceptability possibly high because not connected to individual leprosy cases
- Combination possible with other mass treatment strategies

Strategies: population approach



To be considered:

- Logistically complicated
- Needs tight screening on leprosy, TB and provision of health education
- Introduces wide-spread and less tightly controlled use of antibiotics in a population: *drug resistance!*

Strategies



Considerations regarding SDR:

- Single dose desirable from operational perspective
- Powerful bactericidal drug necessary
- Rifampicin is currently drug of choice
 - Kills at least 90% of viable *M. leprae* at a single dose
 - Well-tolerated
- ROM (rifampicin with ofloxacin and minocyclin) is no more effective, but more expensive and increases risk of side-effects
- SDR insufficient to select resistant mutants: *resistance unlikely*
- **Rifapentin** probably better choice: activity enhanced by intake with food and much longer half-life (15 hours vs. 3 hours)

Strategies



Considerations regarding further research:

- Practical diagnostic tools for detecting sub-clinical leprosy to guide chemoprophylactic treatment in (very) high risk contacts
- Prophylactic treatment regimens needed for (very) high risk contacts
- Epidemiological tools (e.g. mathematical modelling) to evaluate potential effect of chemoprophylactic interventions at population level
- Operational research / health systems research for a successful implementation of chemoprophylaxis at individual and population levels under routine leprosy control programme conditions