The combined effect of chemoprophylaxis with rifampicin and immunoprophylaxis with BCG, in the prevention of leprosy in contacts: a randomized controlled trial

(Funded by MALTALEP 2011-2014)
BCG and leprosy

• BCG vaccine trials, often in combination with *M. leprae* or related mycobacterium vaccines, have shown protective effect against leprosy.

• BCG was as good as, or superior to the other mycobacterium vaccines.

• BCG efficacy appeared to be significantly higher among contacts of leprosy patients than among the general population: 68% vs. 53%.
BCG and leprosy

• The Brazilian government recommends BCG to protect household contacts of leprosy cases.
• A cohort study in Brazil showed that the protection by BCG was 56% and was not substantially affected by previous BCG vaccination.
• The risk of tuberculoid leprosy during the initial months was high among those with no previous BCG vaccination; 21 of 58 new leprosy cases (36%) occurred in the first year.
BCG and leprosy

• This risk had substantially declined by the first year and in the following years the protection rate in this group reached 80%.
• The results of this study are not conclusive due to some methodological inconsistencies.
Chemoprophylaxis with SDR

• A large trial with *single dose rifampicin* (SDR) in contacts of newly diagnosed leprosy patients reduced the overall incidence of leprosy in the first two years with 57%.

• The effect of SDR depended on the BCG status of the contact. If the contact had received BCG vaccination as part of a childhood vaccination program, the protective effect of SDR was 80%.

• Childhood BCG vaccination and SDR both have a protective effect for leprosy in contacts (app. 60%), but if a contact who had previously received BCG vaccination also received SDR, the protective effect is additive.
Objective

• To examine the combined effect of chemoprophylaxis with single dose rifampicin and immunoprophylaxis with BCG, in contacts of new cases of leprosy.

Both interventions are known to have a preventive effect and we hypothesize that these effects may be complimentary, so that the combined effect may be significant and long-lasting.
Design

• Randomised cluster controlled trial comparing immunization with BCG alone with BCG plus SDR in contacts of new leprosy patients.
Intake 1,300 new leprosy patients in Nilphamari, Rangpur, Thakurgaon and Panchagarh districts over 2 years

Exclusion criteria:

- Any patient who refuses examination of contacts
- Any patient who suffers from the pure neural form of leprosy
- Any patient who resides only temporarily in the study area
- Any new patient found during contact examination of the index case
- Any new patient living less than six houses (or less than 100 m) away from a patient already included in the study
- First and second degree relatives of a patient already included in the study
Approximately 15 contacts of each patient are examined

Contacts included:

- Those living in the same house (household members)
- Those living in a house on the same compound, sharing the same kitchen
- Direct neighbors (first neighbors)
Approximately 15 contacts of each patient are examined

**Contacts excluded:**

- Any person who refuses informed consent
- Any woman indicating that she is pregnant
- Any person currently on TB or leprosy treatment
- Any person below 5 years of age
- Any person known to suffer from liver disease or jaundice
- Any person residing temporarily in the area
- Any person suffering from leprosy at the initial survey (these patients will be referred to the clinic for leprosy treatment)
- Any person who is a contact of another patient and is already enrolled in the contact group of the other patient
Randomisation of contact groups into two arms:

- **Arm 1**: BCG only (at 6 weeks after index started MDT)
- **Arm 2**: BCG plus SDR given 8 weeks after BCG
- Each arm approximately 10,000 contacts
**Primary outcome** of the trial: number of leprosy cases in the contact groups of each arm after 1 year

**Secondary outcome** of the trial: number of leprosy cases in the contact groups of each arm after 2 years
Identification of host immune- and gene expression profiles

To identify biomarkers that distinguish individuals controlling bacterial replication from those developing disease, the following assays are used:

1. **Whole blood assays:**

   - venous blood is added to 3 tubes
     - pre-coated with *M. leprae* whole cell sonicate
     - pre-coated with *M. leprae* proteins
     - without stimulus
   - supernatants are analyzed for cellular immune response markers
Identification of host immune- and gene expression profiles

To identify biomarkers that distinguish individuals controlling bacterial replication from those developing disease, the following assays are used:

2. **RNA expression analysis:**
   - RNA is isolated from venous blood
   - Gene expression of >150 target genes is analyzed (by dcRT-MLPA)
**MALTALEP trial**

**Intake**
new leprosy patients
1,300

**Contact investigation**
app. 15/patient

**BCG**
10,000 contacts

1 year: follow-up
new leprosy
Expected: 20

2 year: follow-up
new leprosy
Expected: 8

**BCG + SDR**
10,000 contacts

1 year: follow-up
new leprosy
Expected: 10

2 year: follow-up
new leprosy
Expected: 4

**IDEAL Immunology**
(no intervention)

**Intake**
new leprosy patients
500

**Contact investigation**
app. 10/patient

**Endemic controls**

500

**New patients**

5,000

1 year:
follow-up
new leprosy
Expected: 10

2 year:
Follow-up
new leprosy
Expected: 40

250
Discussion

• Combined chemoprophylaxis and immunoprophylaxis is potentially a very powerful and innovative tool aimed at contacts of leprosy patients that could reduce the transmission of *M. leprae* substantially.

• The trial intends to substantiate this potential preventive effect.

• Evaluation of immunological- and genetic biomarker profiles will allow identification of pathogenic vs. (BCG-induced) protective biomarkers and could lead to effective prophylactic interventions for leprosy by optimizing tools for identification of individuals who should best be targeted for prophylactic treatment.
Partners: