

# Current management of Leprosy

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# Contrast with TB

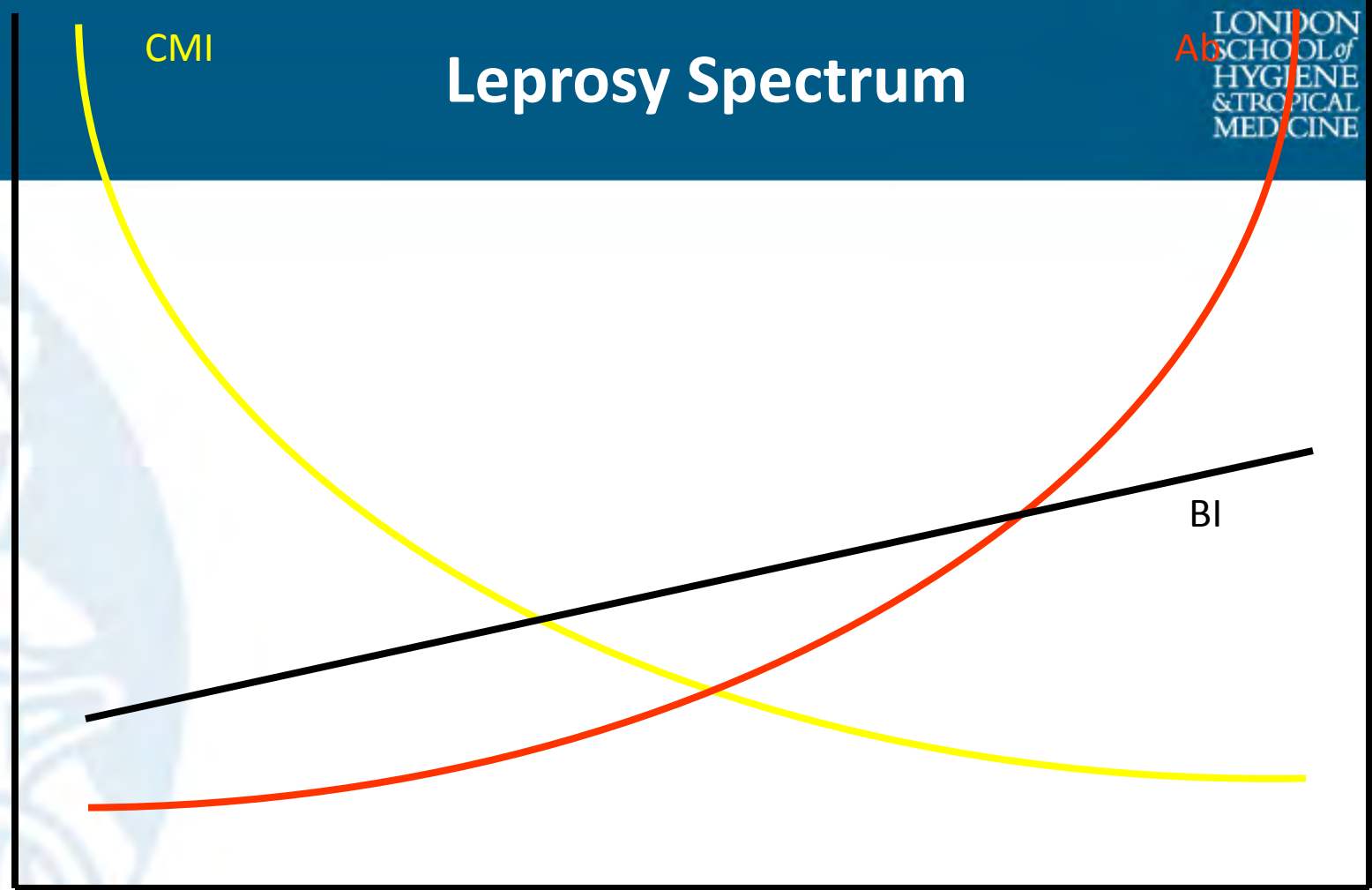
- Effective antibiotic treatment
- Drug resistance is not a problem
- Diagnosis may be more difficult
- Inflammation
  - Skin & nerves
  - Treatment with steroids
  - Difficult to switch off
- Stigma

# Key Facts

- Leprosy caused by *Mycobacterium leprae*
- Type of disease determined by host immune response
- Skin and nerves
- 250, 000 new cases per year
- 16 million completed treatment
- > 3 million with permanent disability
- 194,000 disability adjusted life years
- Women disproportionately affected



# Leprosy Spectrum



TT

BT

BB

BL

LL



Type 1

Type 2

Reversal reactions



Tuberculoid    Borderline    Borderline    Borderline    Lepromatous  
tuberculoid    tuberculoid    borderline    lepromatous    leprosy



# Nerve Damage



**Motor and Sensory function lost**

Claw hand, foot drop, inability to close eyes

Neuropathic injuries



# Diagnosis

- Clinical
  - Skin lesions, peripheral nerve thickening
- Serological tests
  - PGL-1 antibody
  - Specificity ~ 60%
- T cell tests
  - Proving difficult to identify *M.leprae* specific antigens
- No skin tests

# MDT Success Story

- Combination Rifampicin/Dapsone/Clofazimine
  - 2 or 3 drugs 6 or 12 months
- 16 million patients treated since 1982 (Novartis provider)
- Low relapse rates 1%
- Some molecular evidence of drug resistance
  - Rifampicin and Dapsone
- No clinical evidence of resistance being a problem
- Evidence of adverse affects and poor compliance
  - Haemolysis, skin pigmentation
- Need to develop alternative regimens
- Single monthly dose of Rifampicin, Ofloxacin,
  - RCT against WHO-MDT - 6 and 12 months
  - Trial could be done in African centres, add in biomarkers



# Chemoprophylaxis

- Single dose of Rifampicin
- Protection only for wider community
- Not household
- Not multibacillary leprosy
- Only lasted 2 yrs
- Consistent with small effect against low bacterial load

# The INFIR Study In Progress



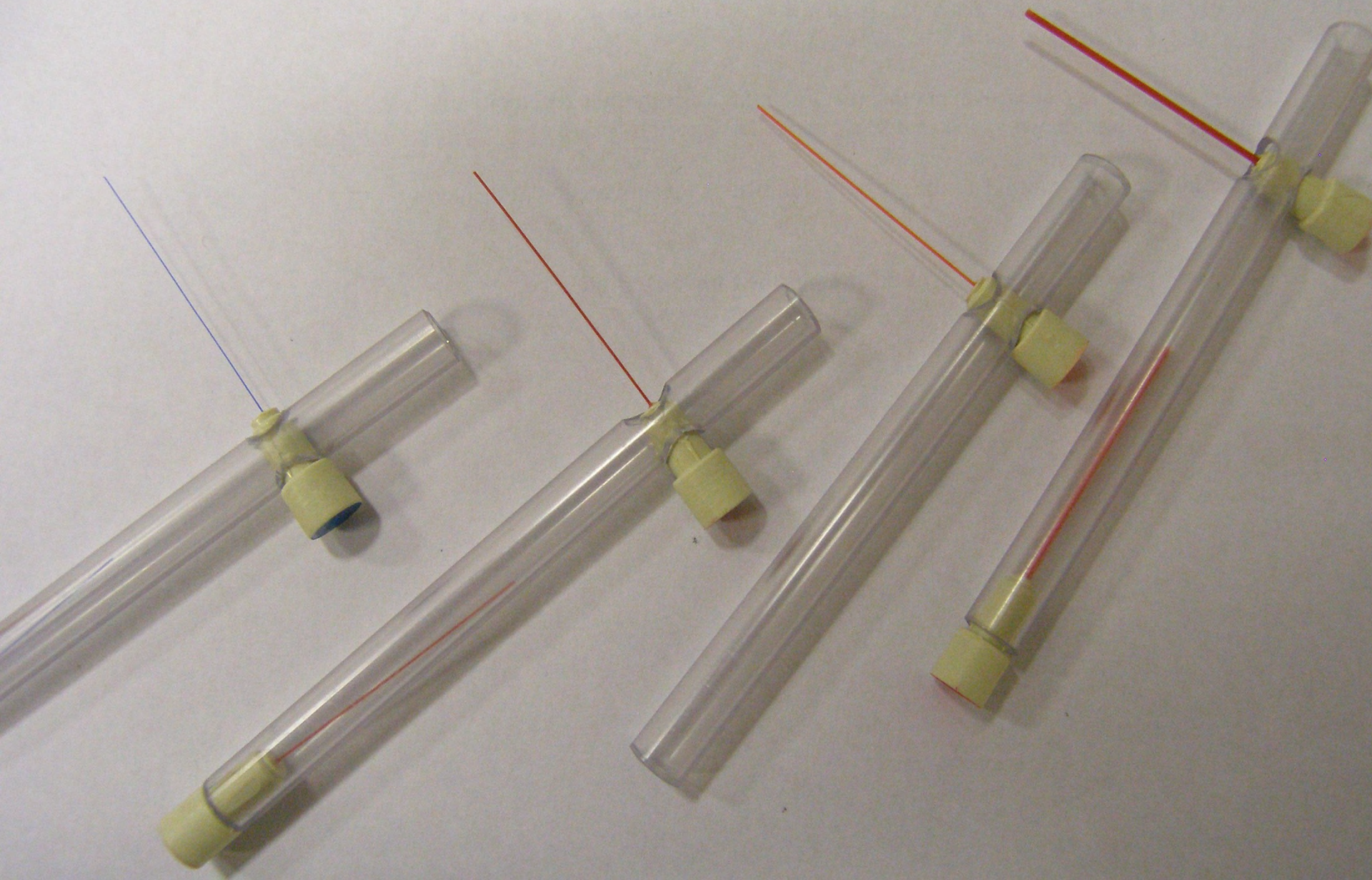
# Nerve Function Impairment

- Motor and sensory loss
- Before, during and after treatment
  - Cohort studies Ethiopia, Bangladesh, India
  - 30 - 56% impairment at diagnosis
- Delay in diagnosis important, > 6 m 60%
- On going studies to identify most sensitive test
  - Temperature

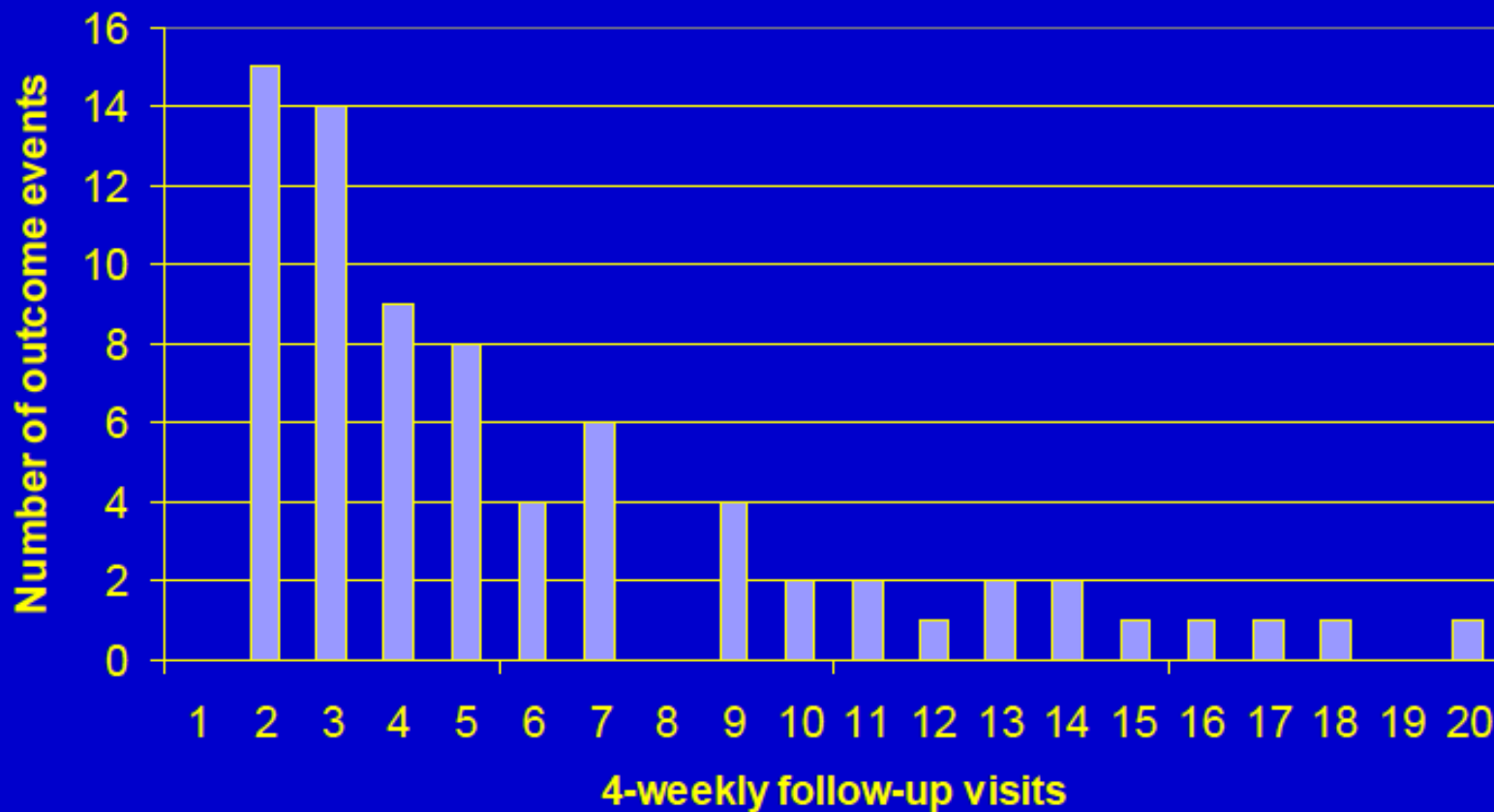




# Neurological Evaluation- Monofilaments for Sensory Testing



# Incidence of outcome episodes in the INFIR Cohort ( $n=188$ )



# Treating Nerve damage and reactions

- Prednisolone 30-60 mg
- 12-24 weeks treatment time, no good data on dose or duration
- Cochrane review only 3 trials could be included

## Outcomes

- Skin - 80% improvement
- Nerves
  - sensory improvement about 50%
  - Motor improvement about 40%
- Relapse rate - 35-50 %
- TENLEP
  1. Comparing 20 vs 32 weeks steroid treatment for nerve damage
  2. Treating patients with subclinical nerve damage.

**Tenlep- multicentre, India, Nepal, Bangladesh. Recruiting finished  
Oct 2013**



# T1R –Second Line agents

- **Needed for patients who do not respond to steroids**
- **Patients who have adverse effects from steroids**
- **Methylprednisolone 1 gm x 3 days then Pred**
  - **No benefit**
- **Azathioprine**
  - **RCT in TLM Hosp N India, placebo, 24, 36 or 48 weeks aza**
  - **No benefit added to steroids from adding in azathioprine**
- **Cyclosporin**
  - **RCT in Ethiopia about to report**
- **Need for new immuno-suppressants**
  - **biologics**

# Neuropathic Pain in leprosy

- 18-25% patients attending leprosy clinics
- Significant cause of depression
- No treatment assessed
- Amytriptyline needs assessing.



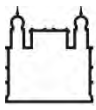
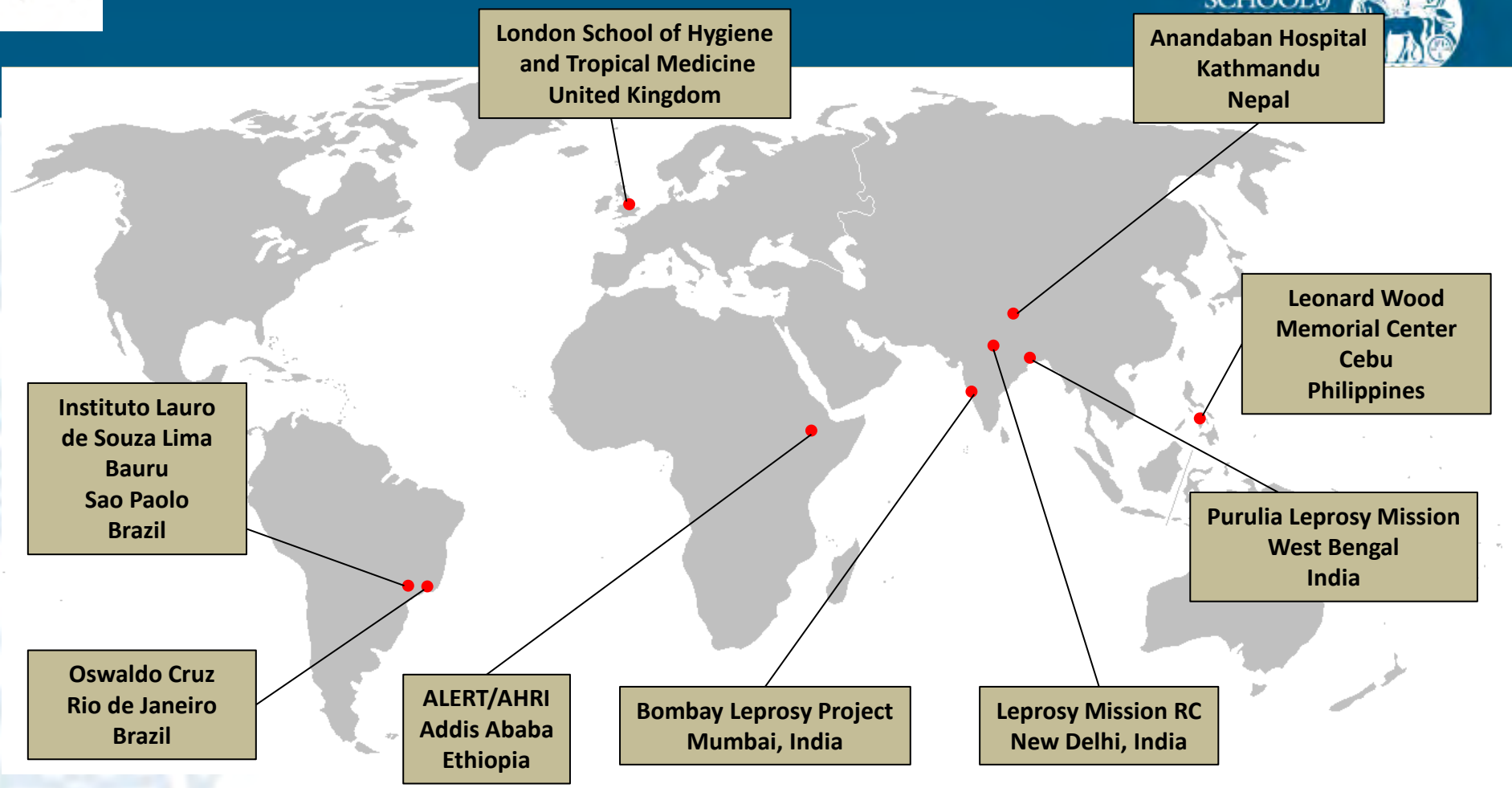
# Erythema Nodosum Leprosum

- **ENL is a multisystem immune complex and T cell disorder**
  - fever, malaise
  - Painful nodules.
  - Bone pain, neuritis
  - Orchitis, iritis,
- **ENL during or after multi-drug therapy (MDT)**
- **treatment with Prednisolone or Thalidomide**
- **ENL is recurrent, lasts years**
- **Death due to steroid adverse effects ( Addis Ababa series)**



# Aims of ENLIST

- Improve understanding of mechanisms causing ENL
- Gather evidence for treatment
- Improve access to treatments
- **Prospective data collection** (7 centres, four continents)
  - Almost 300 patients enrolled
  - Basis for future studies
  - Scientific collaboration, multicentre RCTs



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# Challenges

- Ongoing transmission despite 30 years of effective MDT
- Opportunity RCT of new Multi-Drug Therapy
- Chronic inflammation
- Nerve damage
  - Simple tests
- Predicting which patients will develop nerve damage and reactions
- Immunosuppressants
  - Steroids, identifying which patients respond
- ENL- ENLIST model of global and south-south collaboration
- Stigma
- Early diagnosis still elusive





# Thanks



# Impact of HIV-1 on leprosy

	Theory	In practice
<b>Epidemiological</b>		
– incidence	↑	-
<b>Clinical</b>		
– lepromatous disease	↑	-
– treatment response	↓	-
– type 1 reactional states	↓	↑
– neuritis	↓	↑
<b>Novel Findings</b>		
– Presentation as IRD		
<b>Histopathological</b>		
– granuloma formation	↓	-
– multibacillary	↑	-

# HIV/Leprosy Summary

- HIV infection does not appear to impair local immune response to *M. leprae*
- Patients may present with typical leprosy lesions
- When on HAART then excess BT cases
- Higher risk of Type 1 reactions
- Presentation with IRD
- Treat with MDT
- Long immunosuppression may be needed

## Cochrane Reviews

"Corticosteroids for treating nerve damage in leprosy." Van Veen, N. H., P. G. Nicholls, et al. (2007). *Cochrane Database Syst Rev*(2): CD005491

Interventions for erythema nodosum leprosum. Van Veen NH, Lockwood DN, van Brakel WH, Ramirez J Jr and Richardus JH. *Cochrane Database Syst Rev* 2009 (3):CD006949.

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- WHO Expert Committee Leprosy Oct 2010

# References

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- Shetty VP, Thakar UH, D'Souza E, Ghate SD, Arora S, et al. (2009) Detection of previously undetected leprosy cases in a defined rural and urban area of Maharashtra, Western India. *Lepr Rev* 80: 22-33.
- Moet FJ, Pahan D, Oskam L, Richardus JH (2008) Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ* 336: 761-764.

# Leprosy Epidemiology

- Leprosy technically eliminated as a public health problem 2002 (<1 case per 10 000)
- Under-reporting of cases to meet elimination targets
- Leprosy case figures stabilising in major countries
- Surveys done - many undiagnosed cases
  - Bangladesh PUL 13 /10 000 (Moet 2008)
  - India 3 - 9/10 000, 30% children (Shetty 2009)
  - Hyper-endemic foci
- Policy Implications
  - Ongoing transmission
  - Leprosy resistant to elimination



### Incidence of leprosy in Brazil 1980 - 2008

