

---

# Risk Factors for Nerve Impairment

---

**Peter Nicholls, University of Southampton, UK**

**17<sup>th</sup> ILC, Hyderabad, February 2008**

---

## Outline

- About risk factors
  - Literature review
  - Classified risk factors
  - Validation using the INFIR data
  - Illustration
-

## Identifying risk factors

- **Logistic Regression**

- How outcome relates to predictive variables
  - Death/survival, positive/negative
- **Odds ratios**
  - The increased risk attached to one value of a predictor variable as compared to another

- **Proportional Hazard Regression**

- Includes time adjustment
- **Hazard Ratios**
- **Examples:**
  - Death rates associated with smoking or drinking

## What are the risk factors for nerve impairment in leprosy?

- Search relevant publications
- Indexed by keyword in title or abstract.
  - “Leprosy” plus (“risk” or “factor” or “predict”)
- Focus on clinical rather than genetic or immunological
- At least 32 relevant papers

## Risk factors classified into four groups

- Personal and demographic
- Visible signs
- Advanced stage of nerve involvement
- Others

## Personal and demographic

- Sex
- Age, age >40
- Mode of case finding, passive case finding or self-reporting
- Pregnancy, lactation
- Duration of symptoms , delay > 12 months
- Stress

## Visible signs

- Leprosy group
- Leprosy classification - borderline leprosy
- Smear BI - positive smear
- Number of body areas -  $\geq 3$  body areas
- Number of skin lesions -  $\geq 6$  skin lesions
- Number of enlarged/palpable nerves -  $\geq 2$ 
  - ulnar or lateral popliteal enlargement
- Lesions overlying nerves
  - Specifically facial involvement

## Advanced stage

- WHO Grade 1 and/or WHO Grade 2
- EHF score
- Pre-existing sensory loss
  - By nerve, or in total
- Pre-existing motor loss
  - By nerve or in total

## Other

- Clinical/physical state
  - BCG
  - Tuberculosis
  - Trauma
  - Inter-current infection
  - Time since start of MDT
- Anti PGL1\_IgM seropositivity

## Are these risk factors relevant?

- What population was studied?
  - MB alone, mix of MB and PB
  - Variety of study designs and sample sizes
- What definitions were used?
  - MB/BP leprosy?
  - Which sensory or motor functions assessed and how?
  - What constituted a (treatable) change?
- What coding system and relative frequencies?
- What outcome variable was used in the analysis?
  - RR, NFI within RR, NFI alone (SN), NFI with ENL?

## Are any of them applicable?

- Possibly
  - Could re-analyse BANDS, AMFES, Schreuder/Thailand, INFIR and other data sets
- Following reports risk factors for nerve impairment using the INFIR Cohort Study data set

## The INFIR data set

- 303 cases
- Up to 24 months follow-up – 4,767 visits
- MB leprosy only
- For this analysis:
  - Excluded individuals with baseline reaction
  - 188 individuals, 74 had incident events, 52 included incident changes detected by MF or VMT

## Analysis Methodology

- Cox Proportional Hazard regression using STATA
- Outcome:
  - Incident, treatable change in nerve function detected by MF or VMT
- Univariate analysis of listed predictor variables
  - Stepwise analysis to obtain a simplified predictive model
  
- Health warnings
  - Prefer a larger N.

## Demographic and personal predictors in INFIR

- Age – Increasing age carries greater risk ( $p < 0.001$ )
  - Age groupings above 30 years or 40 yrs also  $p < 0.001$
  
- Sex, delay beyond 12 months, stress – Not sig.
- 
- Variables not available or very small numbers:
  - Mode of case finding, passive or self-reporting
  - Pregnancy, puerperium, lactation

## Visible signs in INFIR

- Count of enlarged nerves ( $p < 0.001$ )
- But none of the following:
  - R classification (BT, BL or LL)
  - Positive smear,
  - $\geq 3$  body areas,  $\geq 10$  skin lesions,  $\geq 2$  enlarged nerves, lesions overlying nerves
  - Facial involvement
- Not available:
  - Leprosy group - no PB cases

## Advanced stage in INFIR

- WHO Grade
  - Grade 1 –  $p < 0.05$
  - Grade 2 –  $p < 0.01$
- EHF score – not statistically significant
- Any pre-existing sensory loss –  $p < 0.001$
- Any pre-existing motor loss – not statistically significant
- Any nerve tenderness –  $p < 0.05$

## Others in INFIR

- Inter-current infection – not statistically significant
- Anti PGL1\_IgM seropositivity – not statistically significant
  
- Not available
  - BCG
  - Tuberculosis – excluded from INFIR study
  - Trauma

## Summary of simple (univariate) predictors in INFIR

- Age
- Pre-existing sensory loss
- Count of enlarged nerves
- WHO Grade 2
  
- Stepwise analysis produces best predictive model

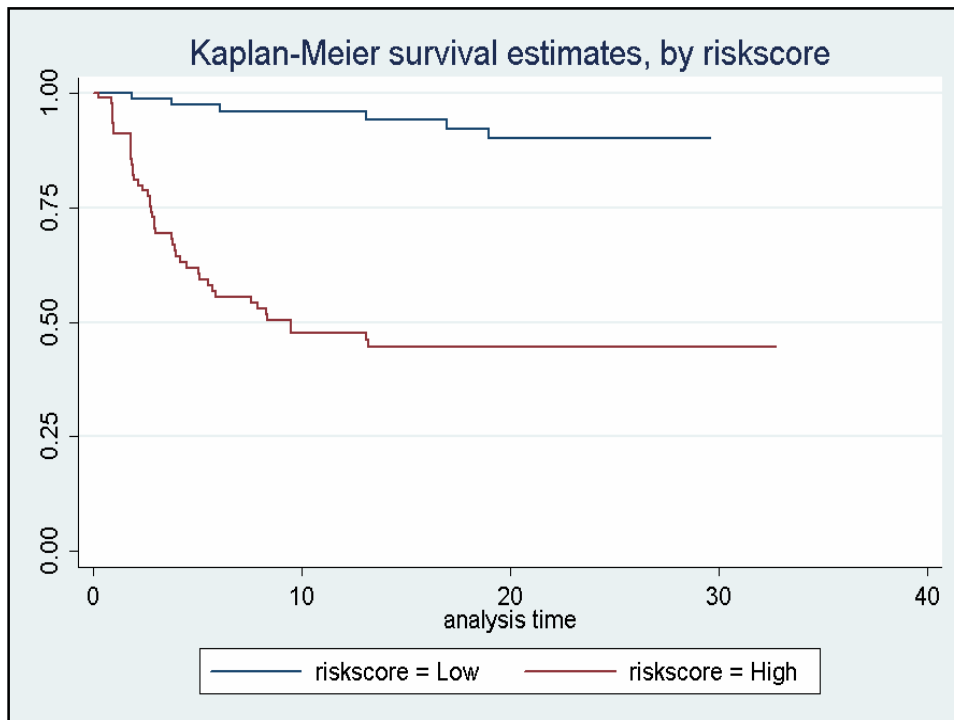
## Predictive model

- Primary risk factors:
  - **Pre-existing sensory loss, HR 4.93 (2.24 – 10.86), p<0.001**
  - **Age > 30 year, HR 3.25 (1.82 – 5.81), p<0.001**
- Secondary risk factors:
  - More than 5 enlarged nerves, HR 2.11 (1.09 – 4.08), p<0.05
  - WHO Grade 1 has a protective effect, HR 0.44 (0.21 – 0.89), p<0.05)
- Approaching statistical significance:
  - Delay less than 12 months
  - More than 10 lesions
  - BT or BL classification
  - High levels of PGL1\_IgM

## Application of the primary model

Number of predictive factors present	Cases with new nerve impairment	Cases with no new nerve impairment	Total (N)
None	6.5%	93.5%	92
One	43.3%	56.7%	67
Two	58.6%	41.4%	29

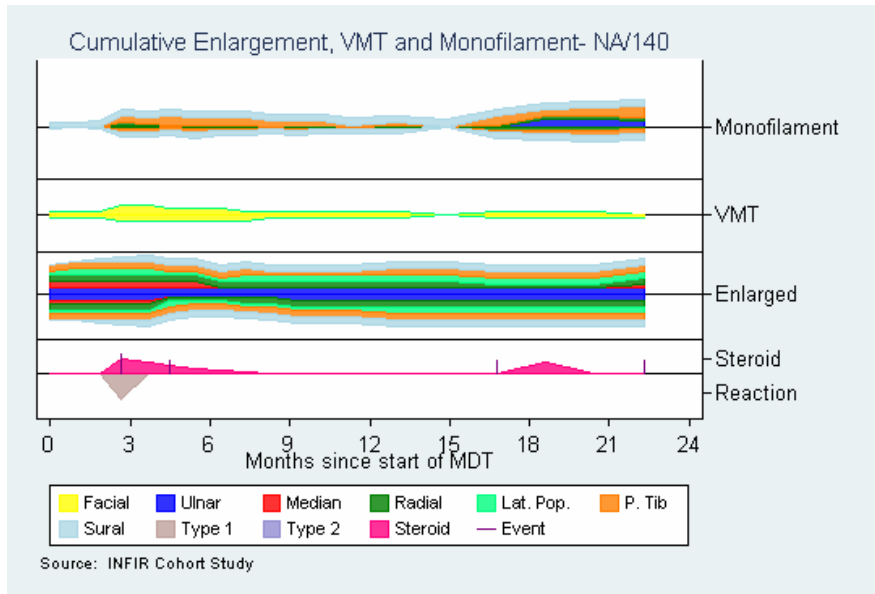
- Identify low and high risk groups



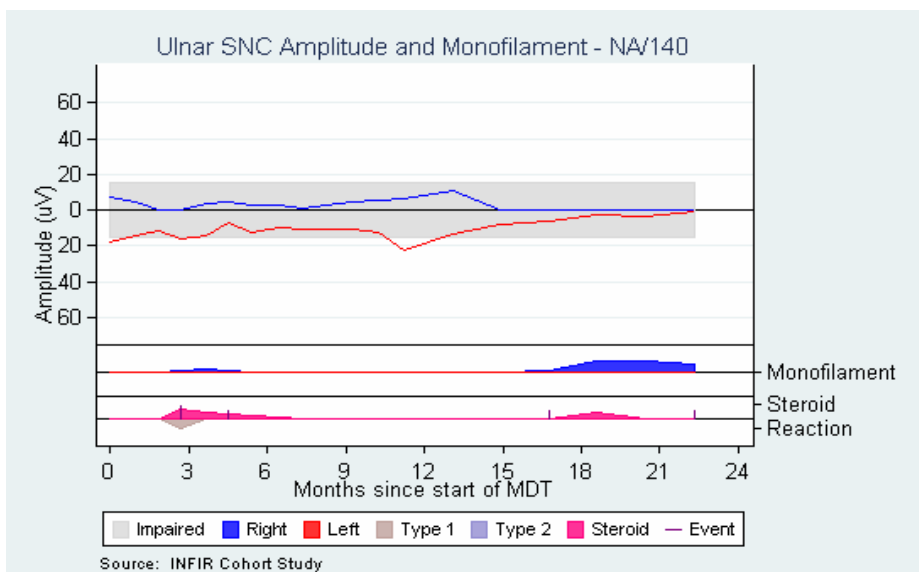
## Additional risk factors identified in the INFIR Cohort Study

- Deterioration in:
  - Ulnar above elbow (proximal) motor nerve conduction amplitude or latency
  - Ulnar, median, radial or sural sensory nerve conduction amplitude or latency
  - Posterior tibial or sural cold or warm sensation

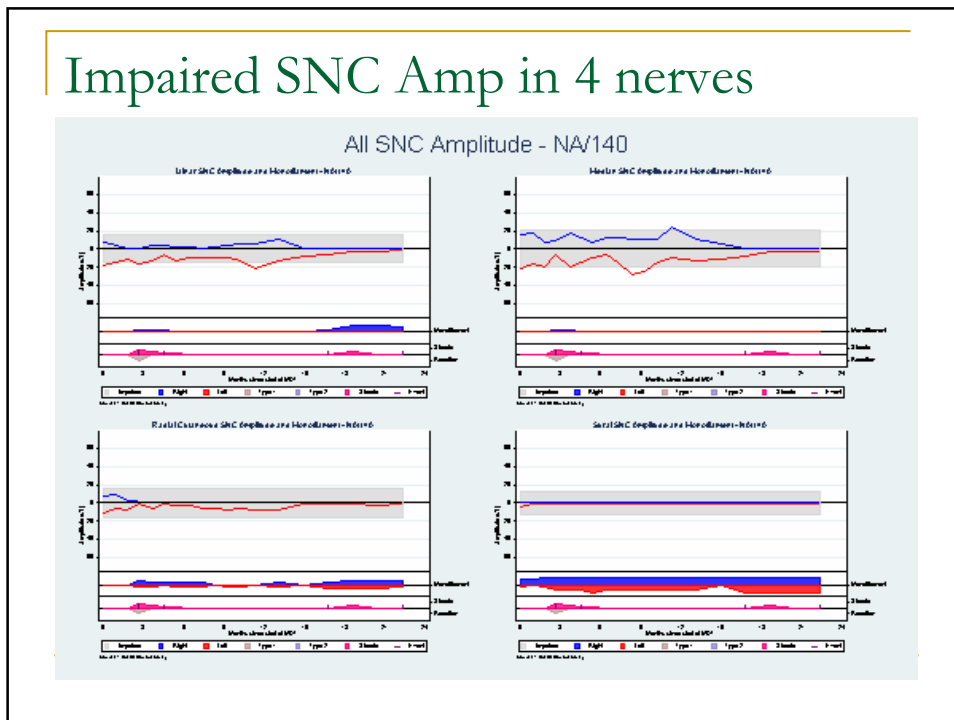
## High risk individual: Male/40/BL



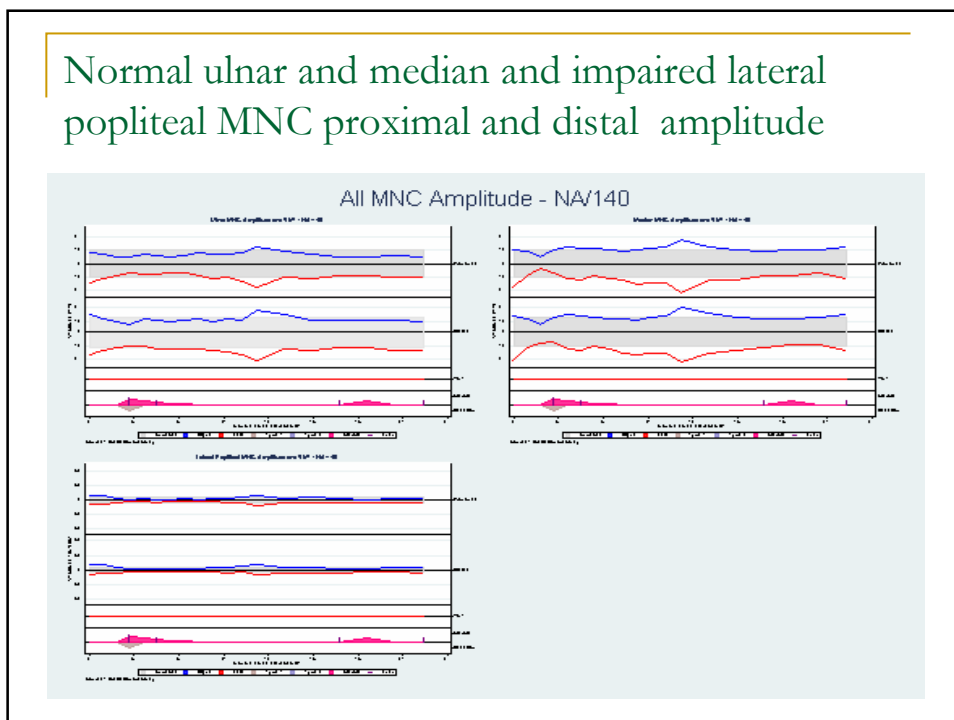
## Sensory loss by MF in ulnar at 18 months.



## Impaired SNC Amp in 4 nerves



## Normal ulnar and median and impaired lateral popliteal MNC proximal and distal amplitude



## Conclusions

- Yes!- We have risk factors for new nerve impairment in MB leprosy:
  - Will vary according to the patient group and definitions
  - For MB, age over 30 years and history of sensory loss at diagnosis are important
  
- BUT, more to this than meets the eye.
  - What measures of nerve status are really important?
  - What implications for detecting, treating and preventing impairment?
  
- Oral Sessions on INFIR Study, Sunday, from 3pm.

## References - 1

1. Lienhardt C, Fine PE. Type 1 reaction, neuritis and disability in leprosy. What is the current epidemiological situation? [see comments]. *Leprosy Review* 1994;65(1):9-33.
2. Mitchell PD. The threshold for protective sensation that prevents neuropathic ulceration on the plantar aspect of the foot: a study of leprosy patients in a rural community in India. *Leprosy Review* 2001;72(2):143-50.
3. Kuipers M, Schreuders T. The predictive value of sensation testing in the development of neuropathic ulceration on the hands of leprosy patients. *Leprosy Review* 1994;65(3):253-61.
4. Smith WC, Anderson AM, Withington SG, van Brakel WH, Croft RP, Nicholls PG, et al. Steroid prophylaxis for prevention of nerve function impairment in leprosy: randomised placebo controlled trial (TRIPOD 1). *Bmj* 2004;328(7454):1459.
5. Richardus JH, Withington SG, Anderson AM, Croft RP, Nicholls PG, Van Brakel WH, et al. Treatment with corticosteroids of long-standing nerve function impairment in leprosy: a randomized controlled trial (TRIPOD 3). *Lepr Rev* 2003;74(4):311-8.
6. Van Brakel WH, Anderson AM, Withington SG, Croft RP, Nicholls PG, Richardus JH, et al. The prognostic importance of detecting mild sensory impairment in leprosy: a randomized controlled trial (TRIPOD 2). *Lepr Rev* 2003;74(4):300-10.
7. Kumar B, Dogra S, Kaur I. Epidemiological characteristics of leprosy reactions: 15 years experience from north India. *Int J Lepr Other Mycobact Dis* 2004;72(2):125-33.
8. Kumar A, Girdhar A, Girdhar BK. Nerve thickening in leprosy patients and risk of paralytic deformities: a field based study in Agra, India. *Lepr Rev* 2004;75(2):135-42.
9. Lockwood DN. Commentary: leprosy and poverty. *Int J Epidemiol* 2004;33(2):269-70.
10. Lockwood DN, Sinha HH. Pregnancy and leprosy: a comprehensive literature review. *International Journal of Leprosy & Other Mycobacterial Diseases* 1999;67(1):6-12.
11. Croft RP, Nicholls PG, Steyerberg EW, Richardus JH, Cairns W, Smith S. A clinical prediction rule for nerve-function impairment in leprosy patients. *Lancet* 2000;355(9215):1603-6.
12. Croft RP, Nicholls PG, Steyerberg EW, Richardus JH, Withington SG, Smith WC. A clinical prediction rule for nerve function impairment in leprosy patients-revisited after 5 years of follow-up. *Lepr Rev* 2003;74(1):35-41.
13. Narang T, Kaur I, Kumar B, Radotra BD, Dogra S. Comparative evaluation of immunotherapeutic efficacy of BCG and mw vaccines in patients of borderline lepromatous and lepromatous leprosy. *International Journal of Leprosy & Other Mycobacterial Diseases* 2005;73(2):105-14.
14. Meima A, Saunderson PR, Gebre S, Desta K, van Oortmarssen GJ, Habbema JD. Factors associated with impairments in new leprosy patients: the AMFES cohort. *Leprosy Review* 1999;70(2):189-203.
15. Nicholls PG, Croft RP, Richardus JH, Withington SG, Smith WC. Delay in presentation, an indicator for nerve function status at registration and for treatment outcome—the experience of the Bangladesh Acute Nerve Damage Study cohort. *Lepr Rev* 2003;74(4):349-56.
16. Pimentel MI, Nary JA, Borges E, Goncalves RR, Samo EN. Impairments in multibacillary leprosy: a study from Brazil. *Lepr Rev* 2004;75(2):143-52.

## References - 2

17. Ranque B, Nguyen VT, Vu HT, Nguyen TH, Nguyen NB, Pham XK, et al. Age is an important risk factor for onset and sequelae of reversal reactions in Vietnamese patients with leprosy. *Clinical Infectious Diseases* 2007;44(1):33-40.
18. Roche PW, Le Master J, Butlin CR. Risk factors for type 1 reactions in leprosy. *International Journal of Leprosy & Other Mycobacterial Diseases* 1997;65(4):450-5.
19. Roche PW, Theuvenet WJ, Britton WJ. Risk factors for type-1 reactions in borderline leprosy patients. *Lancet* 1991;338(8768):654-7.
20. Saunderson P. The epidemiology of reactions and nerve damage. *Leprosy Review* 2000;71(Suppl):S106-10.
21. Saunderson P, Gebre S, Byass P. Reversal reactions in the skin lesions of AMFES patients: incidence and risk factors. *Leprosy Review* 2000;71(3):309-17.
22. Saunderson P, Gebre S, Desta K, Byass P, Lockwood DN. The pattern of leprosy-related neuropathy in the AMFES patients in Ethiopia: definitions, incidence, risk factors and outcome. *Leprosy Review* 2000;71(3):285-308.
23. Schreuder PA. The occurrence of reactions and impairments in leprosy: experience in the leprosy control program of three provinces in northeastern Thailand, 1987-1995 [correction of 1978-1995]. III. Neural and other impairments. *International Journal of Leprosy & Other Mycobacterial Diseases* 1998;66(2):170-81.
24. Schurr E, Alcasis A, de Leseleuc L, Abel L. Genetic predisposition to leprosy: A major gene reveals novel pathways of immunity to *Mycobacterium leprae*. *Seminars in Immunology* 2006;18(6):404-10.
25. Scollard DM, Smith T, Bhoopat L, Theetranont C, Rangdaeng S, Morens DM. Epidemiologic characteristics of leprosy reactions. *International Journal of Leprosy & Other Mycobacterial Diseases* 1994;62(4):559-67.
26. Van Brakel WH, Khawas IB. Nerve damage in leprosy: an epidemiological and clinical study of 396 patients in west Nepal--Part 1. Definitions, methods and frequencies. *Leprosy Review* 1994;65(3):204-21.
27. van Brakel WH, Khawas IB. Silent neuropathy in leprosy: an epidemiological description. *Leprosy Review* 1994;65(4):350-60.
28. Van Brakel WH, Khawas IB, Lucas SB. Reactions in leprosy: an epidemiological study of 386 patients in west Nepal. *Leprosy Review* 1994;65(3):190-203.
29. Van Veen NH, Meima A, Richardus JH. The relationship between detection delay and impairment in leprosy control: a comparison of patient cohorts from Bangladesh and Ethiopia. *Leprosy Review* 2006;77(4):356-65.
30. Waddell KM, Saunderson PR. Is leprosy blindness avoidable? The effect of disease type, duration, and treatment on eye damage from leprosy in Uganda. *British Journal of Ophthalmology* 1995;79(3):250-6.
31. Mpyet C, Solomon AW. Prevalence and causes of blindness and low vision in leprosy villages of north eastern Nigeria. [erratum appears in Br J Ophthalmol. 2005 Jun;89(6):787]. *British Journal of Ophthalmology* 2005;89(4):417-9.
32. Smith WC. Review of current research in the prevention of nerve damage in leprosy. *Leprosy Review* 2000;71(Suppl):S138-44; discussion S145.

## Acknowledgements.

- We are grateful to the people who agreed to participate in this study, attending every month, despite the inconvenience of extensive testing.
- Also to the staff of the TLM hospitals in Naini and Faizabad and the BPRC and Stanley Browne Laboratories.
- We gratefully acknowledge the financial support of Follereau Luxembourg, LEPRU UK and The Leprosy Mission International.