Determinants for the development and course of leprosy: findings from a prospective cohort study

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Summary

This thesis focuses on determinants for the development and course of leprosy. Data were collected as part of the COLEP study—a large, double-blind, placebo-controlled chemoprophylaxis trial, performed in Northwest Bangladesh.

Introduction. Leprosy is a chronic infectious disease that usually affects the skin and peripheral nerves. The subsequent nerve function impairment may progress into the hallmark handicaps and disabilities, despite the availability of effective treatment. For several years the WHO has developed strategies to reduce the incidence and burden of leprosy and sustain the health services in all endemic countries. In chapter 1 gives an overview of aspects of the pathogen *Mycobacterium leprae*, its effect on humans, disease characteristics, progress in disease control, and concludes with a summary of the current research needs. These research needs are discussed per theme in the last chapter using the results from the other chapters when relevant.

Susceptibility. Chapter 2 addresses the influence of host genetics on susceptibility to leprosy and leprosy reactions. Here a polymorphism in a key innate immunity receptor, Toll-like receptor 1 (*TLR1*) N248S, was studied that has been shown elsewhere to diminish TLR1 signaling and subsequent leprosy disease. An alteration in the TLR1 function, or at least in a *TLR1* N248S–linked trait, may affect the progression from infection to disease as well as the disease course and the risk of debilitating reactional episodes in the COLEP study population.

Patient characteristics. Chapter 3 describes patient characteristics and especially their association with the presence of *M.leprae* specific anti-PGL-I antibodies. It concludes that serology is a marker for a higher
systemic bacterial load and gives some recommendations to modify the current skin lesion counting system used for classification and treatment.

*Leprosy reactions.* Leprosy reactions and the accompanying nerve function impairment (NFI) are acute medical emergencies that may occur before, during, and after diagnosis and treatment. The ability to predict and prevent NFI is therefore of utmost importance in the management of patients. In chapter 4 a previously published prediction rule for NFI in leprosy patients is validated and updated. With the described adjusted rule, NFI risk can now be assessed prior to the first event and targeted surveillance can be improved in order to prevent permanent disabilities.

*Prevention.* For prevention of leprosy both BCG vaccination and rifampicin chemoprophylaxis are effective strategies. While the combined effect is unknown, the combination may give the desired push to halt leprosy transmission. Chapter 5 describes the protective additive effect of the combination BCG vaccination and rifampicin chemoprophylaxis.

*Identifying risk groups.* Interventions should be targeted at high risk populations. In chapter 6 the potential of serology, detecting *M. leprae* specific anti-PGL-I antibodies, to identify risk groups is described. Seropositivity and seroconversion of leprosy contacts are shown to be associated with MB leprosy.

*Discussion.* In chapter 7 the results are discussed per research theme as defined by the World Health Organization and its Technical Advisory Group.
Conclusions. The main conclusions drawn are:

- Serological monitoring may help to identify those at higher risk to develop MB leprosy.
- Serology and host genetic factors, ideally combined with markers for cell-mediated immunity in a multiple marker test, may be used to identify leprosy risk groups.
- Determination of lesion size may be a valuable addition to the WHO skin lesion counting system for classification purposes.
- Serology in combination with WHO classification can identify leprosy patients prone to develop NFI. This can improve patient management in general health services.
- Chemoprophylaxis with rifampicin and vaccination with BCG are highly effective as a combination strategy to prevent leprosy, but monitoring of close contacts remains necessary even when both immuno- and chemoprophylaxis are supplied.