

REVIEW

Risk factors for the development of clinical leprosy among contacts, and their relevance for targeted interventions

F. J. MOET*, A. MEIMA*, L. OSKAM** &
J. H. RICHARDUS*

**Department of Public Health, Erasmus MC, University Medical Center Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands*

***KIT (Royal Tropical Institute) Biomedical Research, Meibergdreef 39, 1105 AZ Amsterdam, The Netherlands*

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Summary Existing knowledge on risk factors for the development of clinical leprosy among contacts of known leprosy patients is reviewed with the aim to identify factors associated with leprosy among contacts that have potential for developing effective targeted interventions in leprosy control. Different definitions of ‘contact’ have been used and most studies on this subject were among so-called household members. Yet several studies indicate that contacts found in other places than the household are also at risk of developing leprosy. The type of leprosy and the bacterial index are the main patient-related factors involved in transmission, but also contacts of PB patients have a higher risk of contracting leprosy as compared to the general population. The most important contact-related factors are the closeness and intensity of the contact and inherited susceptibility, while the role of age and sex of the contacts is not clear. The role of socio-economic factors is also vague. The significance of immunological and molecular markers in relation to risk of transmitting or developing leprosy is not yet fully understood, but there is an indication that contacts who are sero-positive for anti-PGL-I antibodies are at increased risk of developing clinical leprosy. The presence of a BCG scar is likely to be related to a lower risk. Analogies with tuberculosis suggest that the ‘stone-in-the-pond’ approach to control may be applicable to leprosy too. Sputum smear negative tuberculosis patients are known to spread the bacteria to others. This analogy strengthens the suggestion that the contacts of paucibacillary leprosy cases should also be included in contact tracing and examination. It is concluded that targeted interventions should be aimed at close contacts of both MB and PB patients inside and outside the household, particularly when genetically related.

Introduction

Contacts of leprosy patients are known to have an increased risk of contracting leprosy themselves. This is not surprising, given the fact that leprosy is an infectious disease caused by *Mycobacterium leprae*, which is spread from person to person mainly through nasal discharges.¹⁻³ Contact tracing has therefore been a regular activity in many leprosy control programmes with the primary aim of (early) case detection and subsequent treatment. However, in infectious disease control in general, contact tracing and examination may have other objectives as well. Finding new cases of sub-clinical infections among contacts offers the possibility to give passive immunization (e.g. hepatitis B) or, in case of non-viral infectious diseases, prophylactic doses of antibiotics (e.g. meningococcal meningitis). These measures can reduce the risk that infected individuals develop a clinical form of the disease with associated complications and prevent further spread of the disease.

In leprosy control it was hoped that providing multidrug therapy (MDT) to all newly detected leprosy cases would not only lead to healing of the patients, but also to prevention of further spread of *Mycobacterium leprae*. Unfortunately, there is no convincing evidence for decreased transmission of *M. leprae*, as the new case detection rate in general has not decreased.⁴ Additional interventions need to be considered, preferably focusing on high risk groups for contracting infection with *M. leprae* and developing clinical leprosy. Prophylactic treatment of contacts is an example of such a possible intervention.⁵ In the absence of a method to determine sub-clinical infection with *M. leprae* reliably, other risk factors for the development of leprosy among contacts need to be identified.

In this paper, we review the literature on data describing the risk of developing leprosy among contacts of leprosy patients and on characteristics of contacts that could be relevant in defining subgroups with different risk levels. Contact definitions will be discussed, followed by a review of potential risk factors. In addition, immunological and/or molecular markers which could be relevant to the development of clinical disease are described briefly. Finally, analogies with tuberculosis are explored as far as these could be relevant for the control of leprosy. The objective of this review is to identify factors associated with leprosy among contacts that have potential for developing effective interventions in leprosy control.

Literature search

First a general literature search using PubMed was carried out using the keywords leprosy, transmission, contact, airborne diseases, tuberculosis and infection transmission either as separate entries or in combination. Then a systematic search using PubMed was carried out for the time period 1940 to 2003, which yielded 253 articles on risk factors and markers in contacts. The Cochrane Library was searched using the keyword strings 'leprosy and contact' and 'leprosy and transmission'. All abstracts that appeared through these searches were scanned on contents, and relevant articles were retrieved. From the references in these retrieved articles, other relevant articles were identified and included into the review.

Definitions of leprosy contacts

One of the first investigations, published in 1942, describing that contacts of leprosy patients had a higher risk of developing leprosy compared to the general population, was

that of Doull *et al.*⁶ in the Philippines. Like Doull's, most later studies on contacts in leprosy were on 'household contacts'. The meaning of 'household' is generally regarded to be understood and no further specification is provided. In a number of studies, however, it is more precisely defined as 'those people living in the same house as the index case',⁷ or 'a group of people sleeping under the same roof and/or partaking food from the same kitchen as the index case'.⁸⁻¹¹ Jesudasan *et al.*¹⁰ divide household members into two categories: (i) those belonging to the nuclear family (parents, children or siblings) and (ii) others. In some studies in Africa another definition was used: 'a group of people considering the same person as (family) head'.^{12,13} Fine *et al.*¹³ divide household contacts into (i) dwelling contacts and (ii) other household contacts, whereby a person was considered a dwelling contact when he or she actually slept in the same dwelling. Amezcua *et al.*¹⁴ divide household contacts into three categories: (i) those living in the same house, but sleeping in a different room, (ii) those sleeping in the same room, and (iii) those sharing the same bed. Ranade *et al.*¹⁵ make a division into 'close' household contacts [wife, (grand)parent and (grand)child] and 'not so close' household contacts (all other). The expression 'bedroom contact' has also been used in contrast with other 'house contacts'.¹⁶ Other studies in leprosy use 'close contacts'¹⁷ or 'family members',¹⁸⁻²⁰ without further defining these terms.

As a matter of fact, the definition and the meaning of the word household are culturally determined. Moreover, within cultures there are likely to be groups where the intimacy of contact within a household differs from the other groups (e.g. rich and poor classes).

White *et al.*²¹ distinguish three groups of contacts: (i) house contacts, actually living in the same house, (ii) compound contacts, living on the same compound but in a different house, and (iii) visiting contacts, living outside the compound. A division into six groups of contacts was made by Van Beers *et al.*:²² (i) household, (ii) neighbour 1 (living directly adjacent to the patient), (iii) neighbour 2 (living next to neighbour 1), (iv) other relative, (v) daily social, and (vi) daily business.

Literature on other infectious diseases frequently describes contacts in rather vague terms such as 'close' and 'casual'. Freudenstein *et al.*,²³ for instance, note that the national (UK) guidelines in the management of tuberculosis do not offer a clear definition of close contact. The Division of Tuberculosis Elimination of the Centers for Disease Control and Prevention (CDC) in the United States has developed practical guidelines for contact investigations which still involve subjectivity: a person with a prolonged, frequent or intense contact with a person with TB while that person was infectious is considered to be a close contact.²⁴ In one study among contacts of tuberculosis patients, close contacts were defined as 'those who slept in the same room, lived in the same house or spent several hours per day with the index case'. The remainder were considered 'casual' contacts.²⁵ In a social network study on AIDS, Klodahl *et al.*²⁶ define 'close personal contacts' as those people who were sharing meals or the same house or clothes and other personal possessions together or were having sexual contact or using drugs together. From these studies it is clear that 'closeness' is also associated with the mode of transmission: close contacts may thus be found in places other than the household of the patient.

It can be concluded that, in describing leprosy contacts, various definitions of contact have been used, based on operational and socio-demographic factors. Definitions of close contacts have primarily been confined to household contacts and have generally neglected close contacts found in other places than the household.

Risk factors and relative risks for developing leprosy in contacts

Studies on risk factors in leprosy have been carried out in the general population and among contacts of leprosy patients. Here we focus on risk factors in contacts. Table 1 lists details of the most important articles describing field studies on contacts. The articles concerning genetics are dealt with in the text, but are not included in the table. The following (potential) risk factors have been identified.

TYPE OF LEPROSY

Over the years the definitions and names of the types of leprosy have been subject to change, which should be taken into account when comparing the results. Doull *et al.*⁶ showed that household contacts of all types of leprosy patients had a relative risk of 6, as compared to the general population, to develop clinical disease. Contacts of 'cutaneous' [*grosso modo* comparable to lepromatous or multibacillary (MB)] patients had an 8-fold increase in risk, whereas for contacts of 'neural' [comparable to tuberculoid or paucibacillary (PB)] patients the risk was four times higher. This study was carried out in the Philippines and included 27,353 person-years with household contact and 307,663 person-years without such contact. Later studies have confirmed the general conclusions that contacts of MB leprosy patients run a higher risk.^{9,10,15,22,27-30} Fine *et al.*¹³ conducted a study in Malawi including 8741 contacts living in 1656 households among a population of 80,451 people, and found that dwelling contacts of MB patients had a greater risk of contracting the disease than other household contacts, while such a difference was not seen for contacts of PB patients. By dividing PB cases into those whose bacteriological index (BI) was zero and those whose BI was one (presently by definition MB patients), they found evidence that contact associated risk is positively related to the BI.

INTENSITY OF CONTACT AND PHYSICAL DISTANCE TO A LEPROSY PATIENT

Sundar Rao *et al.*²⁸ (India, the study included 40,625 contacts) found a higher risk for household contacts of leprosy patients as compared to the general population (whereby the contacts of MB patients run a higher risk than those of PB cases). The same was reported by Van Beers *et al.*²² from Indonesia, where they did a retrospective and non case-controlled study, in which they also found that 28% of the 101 new leprosy cases they evaluated, could be classified as household contacts. If they included neighbour contacts as well, 63% could be classified as contacts. Another 15% could be connected to another leprosy patient if social contacts were included. These figures indicate that at least 78% of new leprosy patients could be connected in place and time to a previously diagnosed leprosy patient. The relative risk of household members was 9.4; of neighbour 1 (those living in the house next to a patient) 4.0; and of neighbour 2 (living in a house next to neighbour 1) 1.6. The relative risks for contacts of MB patients were higher than for contacts of PB cases. In the Philippines Cunanan *et al.*³¹ found an even higher relative risk in household contacts: 26 (95% confidence interval 8-84) as compared to non-household contacts. This study included 2087 household contacts and 4750 'community' contacts.

In India, Jesudasan *et al.*¹⁰ and Vijayakumaran *et al.*²⁹ studied 9162 and 1661 contacts, respectively, and reported that close household contacts (parents, siblings and children) have a higher risk of contracting leprosy than other household contacts. Several authors also found

Table 1. Publications on risk factors for developing leprosy among contacts

Reference	Design	Contact definitions	Study population	No. index cases or households	Time of follow-up	Risk factors considered	Outcome indicators
Doull <i>et al.</i> ⁴⁴ (Philippines)	Retrospective contact study	A person who had lived under the same roof as a leprosy patient for at least one month	1520 contacts out of a population of 16,557	Unknown	19,553 PYR	Age of contact at exposure; sex of contact	Annual incidence per 1000 PYR
<p>For those exposed before the age of 5, the male/female incidence ratio in all age groups is > 1. The younger the age group the more males predominated (male/female ratio 4.7/1 for the age group of 5–10, and 1.4/1 for the age group of 20 years and over). The age of initial exposure is inversely related to the risk of developing lepromatous leprosy.</p>							
Ali <i>et al.</i> ²⁷ (India)	Prospective contact study	Family members living with the patient	14,776 contacts	4383 cases (in 3666 families, of which 3104 single patient)	2 years	Age of contact; sex of contact and index; type of leprosy and BI of index; number of co-prevalent cases	Attack rate (AR) per 100 per year
<p>Contacts of lepromatous patients suffer the highest attack rate (AR). The AR in two-source families is almost double that in single-source families. The AR decreases with age of the contact. The AR among females is lower than among males.</p>							
Rao <i>et al.</i> ⁹ (India)	Prospective contact study	Those partaking food from the same kitchen and sleeping under the same roof	22,652 contacts	5088 families (4422 single patient families)	77,159.5 PYR	Age of contact at exposure; sex of contact; type of leprosy of index; number of co-prevalent cases	Secondary attack rate (SAR) per 1000 PYR
<p>The secondary attack rate (SAR) among females and males did not differ significantly. SAR by age at exposure was highest among the age group of 5–9 ($P < 0.01$). SAR almost doubled when there were multiple cases in the family. SAR among contacts of lepromatous patients was 9.5 whereas the SAR among contacts of non-lepromatous cases was 5.8.</p>							

TABLE 1 – continued

Reference	Design	Contact definitions	Study population	No. index cases or households	Time of follow-up	Risk factors considered	Outcome indicators
Jesudasan <i>et al.</i> ¹⁰ (India)	Retrospective contact study	Refinement of Rao 1975: same definition of household but divided into two groups: 1. member of nuclear family (parent, sibling, child); 2. others	9162 contacts with 228 incident cases	1564 'primary cases'	60,423 PYR	Age of contact: BI of 'primary case': number of co-prevalent cases: closeness of relation	Incidence rate per 1000 PYR: relative risk compared to general population
<p>Household contacts of non-lepromatous patients had a lower incidence rate as compared to contacts of LL and BL patients ($P < 0.05$). The relative risk of household contacts of non-lepromatous patients was 2.2 and of BL and LL cases 3.1 as compared to the general population. The age specific incidence rate among household contacts reached a peak in the age group of 5–9 years. The presence of co-prevalent cases (patients in the household diagnosed as having leprosy at the first survey) increased the incidence rate in that particular household significantly. Close household contacts (contacts closely related to the primary case as members of a nuclear family such as parent, child and sibling) have a relative risk of 2 compared with other household contacts.</p>							
Sundar Rao <i>et al.</i> ²⁸ (India)	Retrospective contact study	Same as Rao 1975 and Jesudasan 1984	40,625 contacts	8642 'primary cases'	176,183 PYR	Age of contact: sex of contact: type of leprosy of index	Incidence rate (IR) per 1000 PYR: relative risk compared with general population
<p>The peak incidence rate (IR) is in the age group 5–9 years. The IR among contacts of adult primary cases was significantly higher than the IR among the contacts of child cases ($P < 0.01$). Household contacts of MB cases have a relative risk (RR, as compared to the general population) of 3–6 whereas the contacts of PB cases have a RR of 2–4.</p>							
Ranade <i>et al.</i> ¹⁵ (India)	Retrospective contact study	Household ('group of people living under the same roof and partaking food from the same kitchen'). Two categories: 1. close relation: (grand)parent, spouse, (grand)child; 2. others	6284 contacts	1184 'primary cases'	74,174 PYR	Sex of contact: closeness of relation: length of contact period: type of leprosy of index: treatment compliance of index	Attack rate (AR); relative risk

TABLE 1 – continued

Reference	Design	Contact definitions	Study population	No. index cases or households	Time of follow-up	Risk factors considered	Outcome indicators
<p>The attack rate (AR) for male contacts significantly higher than for female contacts. No significant difference in AR between close and not close contacts. No indication that duration of contact influences the AR. Positive correlation between BI of index and AR among contacts. Regularity of treatment taken by index had no significant effect on the AR among contacts.</p>							
Fine <i>et al.</i> ¹³ (Malawi)	Prospective contact study	Household = group of people recognizing one person as their head, with two categories: 1. dwelling contacts: sleeping in the same dwelling; 2. other household contacts	8741 contacts living in 1656 households among a population of 80,451 people	1887 cases	423,630 PYR (total population regarded as 'at risk')	Level of contact by: age of contact person; sex of contact person; type of leprosy of index; BCG scar of contact	Incidence rate ratio
<p>Relative risk (RR) of household and dwelling contacts of MB patients is 5–8 as compared to the general population. RR of contacts of PB patients is 2. Dwelling contact with MB cases is associated with a higher risk than just household contact. This association is not seen for contact with PB cases. The risk of disease was inversely related to the age of the contact [$P = 0.08$ (MB)–0.14 (PB)]. Male contacts had a higher risk than female contacts [$P = 0.05$ (MB)–0.72 (PB)]. RR of individuals without a BCG scar compared to individuals with a scar was 4.8 for MB contacts (95% confidence interval (CI) 2.1–10.9) and 1.8 for PB contacts (CI 1.2–2.6).</p>							

TABLE 1 – continued

Reference	Design	Contact definitions	Study population	No. index cases or households	Time of follow-up	Risk factors considered	Outcome indicators
Vijayakumaran <i>et al.</i> ²⁹ (India)	Prospective contact study	Household contacts divided into two groups: 1. Contacts before MDT of index (original cohort) 2. Contacts after index started on MDT (additional cohort)	1,661 (1094 original cohort, 567 additional cohort)	337 cases	8,403 PYR	Age of contact; sex of contact; BI of index; presence of co-prevalent cases; index on MDT	Incidence rate per 1000 PYR; relative risk
<p>The original cohort had a higher risk than the additional cohort (relative risk = 2.85, $P = 0.001$), Children (up to age 14) had a higher risk than adults ($P = 0.001$), No gender difference was seen.</p> <p>Contacts of patients with a bacterial index (BI) of >2 had a relative risk of 3.01 as compared to contacts of patients with a BI <2 ($P < 0.001$).</p> <p>The presence of a co-prevalent case in the household increased the incidence among the original cohort (from 7.5 to 13.4 per 1000 person years of observation (PYR)) ($P < 0.001$).</p> <p>The incidence rate (IR) among the general population was 0.9 per 1000 PYR, the IR among the original cohort was 9.1 and the IR among the additional cohort 4.2.</p>							
Cunanan <i>et al.</i> ³¹ (Philippines)	Prospective population survey	1. Household contacts ('presence of index case at home'); 2. Community contact ('other contact')	2087 (household); 4750 (community)	37 new cases	6 years	Type of contact; seropositivity (Elisa)	Relative risk
<p>The relative risk (RR) of household contacts developing leprosy was 26 times greater than of community contacts (95% confidence interval 8–84). The RR of ELISA(+) contacts was 24 compared to ELISA(–) contacts (95% CI 12–45).</p>							
De Matos <i>et al.</i> ³⁰ (Brazil)	Prospective cohort study	Household contacts	758 contacts	Unknown	4 years	Positivity of Mitsuda skin test of contact; prior BCG vaccination of contact; type of leprosy of index	Incidence rate per PYR; odds ratio for risk of developing leprosy
<p>The risk was related to the multibacillary form of leprosy in the index case: odds ratio (OR)=2.547; CI 95%=1.249–5.192. Prior BCG vaccination was related to a lower risk: OR = 0.3802; CI 95% = 0.2151–0.06672. A negative Mitsuda skin test was associated with an increased risk: OR = 3.093; CI 95%=1.735–5.514.</p>							

TABLE 1 – *continued*

Reference	Design	Contact definitions	Study population	No. index cases or households	Time of follow-up	Risk factors considered	Outcome indicators
Van Beers <i>et al.</i> ²² (Indonesia)	Retrospective study	Six categories: (1) Household, (2) Neighbour 1, (3) Neighbour 2, (4) Relative, (5) Social (daily), (6) Business (daily)	2283 (total population)	101 cases	25 years	Type of contact; type of leprosy	Rate ratio; relative risk

The rate ratio (defined as the incidence in contact households divided by the incidence in non-contact households) of household contacts was 9.4 (CI 95% = 5.7–15.7), of first neighbours 4.0 (CI 95% = 2.4–6.9) and second neighbours 1.6 (CI95% = 0.8–3.0).

The relative risk of household contacts of MB patients is 13.7, and of PB patients 5.2, as compared to members of households without any leprosy patient.

PYR = Person years at risk.

BI = Bacteriological index.

BCG = Bacillus Calmette et Guérin.

that the attack rates in households with more than one leprosy patient were twice that of families with only one case.^{9,21,27,29} As already mentioned, Fine *et al.*¹³ state that being a dwelling contact of an MB patient is associated with a greater risk of contracting leprosy than being another household contact. It has been argued that family size was relevant, reasoning that the greater the crowding, the more intimate the contact, and it was also suggested that 'bedroom contact' bears a greater risk than other 'house contacts'.¹⁶ Both suggestions could not be confirmed by Newell.³²

Hausfeld tried to measure exposure in leprosy and described an anthropological method which was used in New Guinea.³³ This method took into consideration that contacts are not limited to households and that the social structure of the community will reflect the transmission and distribution of the disease. A scoring system was developed in order to differentiate between various levels of intensity of contacts. When this method was applied to their study population, it was shown that the incidence of new cases increased rapidly with the closeness of the known level of contact with a lepromatous case.

In summary, it has been established that being a contact of a leprosy patient is a risk factor for contracting leprosy, the extent of the risk being dependent on the closeness of contact. Household contacts (those living in the same house and sharing the same facilities) appear to have the highest risk, but an increased risk for leprosy is not limited to household contacts alone.

GENETIC FACTORS

The risk of developing clinical leprosy is thought to be partly determined by hereditary factors.³⁴⁻³⁹ Most contact studies in leprosy refer to household contacts. As household contacts often share a common genetic background, differences in risk as compared to the general population, could at least in part be attributed to one or more genetic factors. White *et al.*²¹ showed in Uganda where they followed 20,990 children over a period of 8 years, that apparent clustering among closest relatives could well be explained by the more intimate household contact alone and they concluded that if a genetic component of susceptibility existed, it would have a minor influence. They note, however, that in their study group the number of children with contact with a lepromatous patient was too small to draw conclusions on this subgroup. In a review on genetics in leprosy, Beigelman concluded that '*consanguineous relatives of lepromatous cases are proner to the same form of leprosy than nonconsanguineous relatives (spouses)*'.³⁴ A study in Papua New Guinea among the members of 269 leprosy kindreds showed that leprosy was family related in a population in which the family was not the basic social unit,³⁵ but Ranade *et al.*,¹⁵ in India, in another retrospective contact study among 6284 contacts of 1184 leprosy patients, could not find a statistically significant difference in risk of developing leprosy between closely related contacts and those not closely related. A study on twins in India showed that the concordance (the probability that the other of the twins develops disease if one is affected) is more than twice as high in monozygotic twins as in dizygotic.⁴⁰ More recent studies concluded that both HLA (DR2) and non-HLA (SLC11A1, formerly NRAMPI and TNF α) genes contribute to a genetic susceptibility to either leprosy *per se* or a type of leprosy.⁴¹⁻⁴³ Fitness *et al.*³⁷ reviewed this topic in 2002 and concluded that several genes may be involved in susceptibility to leprosy *per se* or to a type of leprosy, but because many of the associations have only been found in small series of patients or in a single population, these findings would need confirmation in larger studies.

A year later, Mira *et al.*³⁹ published the results of a study in Vietnam among 86 families affected by leprosy. They found that a locus on chromosome 6q25 appears to control part of the susceptibility to leprosy *per se* with a maximum likelihood binomial lod score of 4.31, $P = 0.000005$. This study also confirmed the results of an Indian study showing that a locus on chromosome 10p13 is linked to paucibacillary leprosy, with a maximum lod score of 4.09, $P < 0.00002$.³⁸

In conclusion it can be stated that there is accumulating evidence that the risk of developing leprosy is partly genetically determined, although this is as yet not fully quantified. This genetic predisposition could, at least to some extent, explain the observed increased risk to develop leprosy among family contacts of leprosy patients. The contribution of genetic predisposition to the development of leprosy still remains to be disentangled from the effect of relatives living together closely.

AGE AND SEX

Age is found to be a potential risk factor for contacts to develop leprosy. Several authors found that, among the household contacts of MB patients, the risk for children less than 14 years of age was substantially higher than that for adults.^{9,10,13,27–29} Three of these studies mention a peak rate between the age of 5 and 9 years, but are all referring to the same study population.^{9,10,28} Doull *et al.*⁴⁴ reported in 1945 from the Philippines that there was a relation between risk of developing clinical leprosy and the age of initial exposure, the risk decreasing with age of exposure. Noordeen on the other hand states that in high endemic areas like South India (the study of Vijayakumaran was also conducted in South India²⁹) the age-specific incidence shows a bimodal distribution with a peak at age 10–14, followed by a depression that is again followed by a rise and a plateau over the ages 30–60, which is higher than the first peak.⁴⁵ He bases this on figures of the WHO. A possible explanation for these seemingly contradictory findings could be the difference in definitions of the age groups as in several studies all people older than 14 are lumped together as adults, while this group is further subdivided in the WHO data.

Considering gender, there have been conflicting findings. Vijayakumaran *et al.*²⁹ found no gender difference, which is consistent with the study of Rao *et al.*,⁹ but is in contrast with a study in Malawi where it was found that the risk was significantly greater for males than for females. In an early Indian study, Ali *et al.*²⁷ also noted that the attack rate in female contacts was lower than in the male contact group. This was observed by Doull *et al.*⁴⁴ and by Ranade *et al.*¹⁵ as well.

Several explanations have been proposed for differences in gender related incidence. One might be the differences in diagnostic activities among the two sexes (ascertainment bias). It could also be that men are more exposed to infection as they clothe differently and have more contact with other people. A biological difference cannot be ruled out.⁴⁵

In summary, age and sex have both been shown to be potential risk factors with higher risks seen in young children and older adults as well as in males.

SOCIO-ECONOMIC FACTORS

Socio-economic factors could also be of some importance in determining the risk of developing leprosy. Pönnighaus *et al.*¹² showed a strong inverse relation between the number of completed years of schooling and the leprosy risk, and that good housing conditions were

associated with a decreased risk. In contrast, Ali did not find a relation between risk of contracting leprosy and socio-economic factors such as sanitation, housing conditions, economic status, literacy and nutrition.⁴⁶ These two studies were carried out in totally different communities and the results are therefore difficult to compare. Moreover, these studies were population studies, not focused on contacts. If socio-economic factors influence the risk of developing leprosy in general, it does not necessarily mean that adverse socio-economic conditions, once a patient has been identified, increase the risk for the contacts. In airborne diseases in general, however, indoor air quality is a factor that influences the risk of transmission,⁴⁷ so it may be assumed that this may also be the case in leprosy.

Immunological and molecular markers

Serological and immunological tests could be helpful in defining groups of contacts at higher risk of developing leprosy, partly because the results of these tests may be an indication of sub-clinical infection. Several studies have shown that antibody levels can be used as a surrogate marker for the bacterial load in the sense that there is a positive correlation between antibody levels and the bacterial index.⁴⁸ For a state of the art overview on serology we refer to a recent article by Oskam *et al.*⁴⁹ They state that subclinical infection is far more common than overt disease as antibodies against *M. leprae* can be detected in 1.7–31% of the endemic population. They conclude that serology cannot be used as a single diagnostic test for leprosy, nor can it be used for population screening or for distinguishing past and present infection. It can be used, however, for classification purposes.

From a prospective field study in French Polynesia among 1201 family contacts over a 10-year period, Chanteau *et al.*²⁰ concluded that the presence of anti-PGL-I antibodies has a low predictive value for the early diagnosis of leprosy in family contacts (2% risk for seropositive contacts as compared to 1% for seronegative contacts, $P = 0.2$), although the preliminary results after 2 years of the trial suggested that there was such a relation.⁵⁰ In contrast, Ulrich *et al.*⁵¹ found in a prospective study in Venezuela among 29,000 household contacts, that anti-PGL-I antibody levels indicate a significantly higher risk of developing leprosy in the next 4 years, $P < 0.001$, but that the test would be of very limited value as a screening test in control programmes because of the low sensitivity and specificity. As this study was carried out in the context of a vaccination trial, the results should be regarded with caution as the vaccination could have altered the immune response. Douglas *et al.*⁵² (Philippines) gave preliminary results after 2 years of follow-up of 321 household contacts and 401 controls, stating that the presence of anti-PGL-I antibodies in contacts of MB patients indicated an increased risk of developing leprosy, and in particular MB leprosy: the attack rate for seropositive contacts was 8.3% while the attack rate for seronegative contacts was 0.4%. They also found that only a minority (18%) of MB cases gave rise to sero-reactivity among their contacts. Cunanan *et al.*³¹ found in a study among 6837 contacts, also in the Philippines, that seropositive contacts had a 24-fold increased risk of developing leprosy (95% CI 12–45).

The lepromin test is regarded as a marker for the cellular immunity against *M. leprae*.⁵³ This test is unfortunately not a good indicator of active or recent infection as in leprosy the specific cellular immunity can be absent, especially in patients with lepromatous disease and the test can be falsely positive due to cross-reactivity between *M. leprae* and other mycobacteria.⁵³ Some studies have been carried out combining lepromin reactivity and

measurement of antibodies against *M. leprae*. Dayal *et al.*⁵⁴ found in India, in a prospective study among 455 initially healthy child contacts of different types of leprosy patients, that those children who were antibody positive and lepromin negative had a significantly higher risk of developing leprosy than the other children ($P < 0.01$).

Trials and case-control studies with Bacillus Calmette et Guérin (BCG) vaccine both in the general population and in contacts of leprosy patients have indicated that this vaccination gives partial protection against the development of leprosy, especially when administered repeatedly.^{55–58} The protective effect of BCG vaccination is remarkably consistent in the general population as well as in contacts and is present in countries in South America, Africa and Asia.⁵⁹ Although the magnitude of this protective effect differs considerably between the studies, from 20–80%, it is likely that BCG vaccination (indicated by a scar) represents a lower risk.

Pattyn *et al.* examined the presence of specific *M. leprae* DNA in nasal swabs of a small group of contacts of leprosy patients on the Comores by means of the polymerase chain reaction (PCR).⁸ There was no significant difference between the contacts of PB and MB patients (1.9% and 7.9%, respectively, $P = 0.20$), and it was concluded that the observed infection was community-acquired. De Wit *et al.*⁶⁰ (Philippines) found that 19% of the occupational contacts of leprosy patients ($n = 31$) were PCR positive while in the general population this percentage was 12 ($n = 25$). This difference was not statistically significant. In a study in Indonesia, transient positive PCR-tests were observed in 7.7% of nasal swabs obtained from sero-negative individuals in the general population.⁷ A correlation between PCR positivity and serology could not be demonstrated.

It can be concluded that immunological and molecular techniques are as yet incapable of identifying individuals with a sub-clinical infection. There is an indication that contacts who are sero-positive for anti-PGL-I antibodies are at increased risk of developing clinical leprosy.

Analogy with tuberculosis

Tuberculosis and leprosy share several characteristics. Both are (at least in part) airborne mycobacterial diseases with a long incubation period. Cellular immunity is necessary to combat both diseases. Moreover, both diseases are capable to give rise to re-infection and relapse. Some of the knowledge from studies in tuberculosis could be relevant for leprosy as well. To date more is known about transmission patterns in tuberculosis, partly because of the availability of molecular epidemiological methods. DNA typing techniques for leprosy are still under development as heterogeneity loci were only identified recently, but developments in this field are going fast. The possibility to use molecular epidemiology will allow a better understanding of transmission patterns, as witnessed by findings from Matsuoka *et al.*⁶² that infection of household members is not necessarily caused by the patient living in that household.

DNA fingerprinting in tuberculosis research made clear that transmission of this disease outside households to other people than close contacts is far more important than previously believed.⁶³ In a study in San Francisco, it was found that only 10% of the patients who were linked according to fingerprinting techniques, would also have been identified by conventional contact tracing.⁶⁴ Klovdahl *et al.*⁶⁵ suggests that outbreak investigations could be more effective if these were not only person oriented ('case-finding'), but also place

oriented ('place-finding'), as other places than private households may be involved in outbreaks.

Marks *et al.*⁶⁶ reported a gradual decrease in tuberculin skin test (TST) positivity from contacts belonging to the household, via leisure contacts, relatives not living in the same household and work contacts to other contacts of pulmonary, acid-fast bacilli (AFB) sputum smear (+) TB patients. Beside the distance to the source, source-related factors were found to be important, like the presence of a cavity and high sputum smear positivity. These results were in general consistent with those found by Del Castillo Otero *et al.*²⁵ in their study in Spain. In this study, it was also found that not only smear positive patients may transmit the disease, as 43% of the contacts of patients with negative bacteriological results were also infected. This could partly be explained by the fact that there were other close sources who might have caused TB in the index case and infected other contacts as well. Menzies also stresses that contagiousness is not an all-or-nothing phenomenon, depending on more factors than the sputum status alone.⁶⁷

The knowledge about the transmission of tuberculosis and the role of contacts therein raises a number of important and yet unanswered questions for leprosy. These will be addressed in the discussion section.

Discussion

In the literature on leprosy, many different definitions of 'contact' have been used which are based on operational considerations. It can be concluded that people at risk of contracting leprosy are not confined to the group of direct family members living under the same roof, which is the group of contacts currently examined during contact surveys in many leprosy control programmes. Contact events are likely to be more frequent and intense in this group and a higher risk has been demonstrated, but neighbours and social contacts appear to be important contact groups as well. The available data suggest that the risk of contracting leprosy decreases with increasing physical distance to the patient. This hypothesis needs further substantiation because only few studies looked beyond the level of the household in defining contacts.

In order to make maximum use of other sociological parameters of the study population, a scoring system of levels of contact, as described by Hausfeld,³³ would be ideal. However, computer-supported anthropological research among the population concerned would be needed first, which is very time consuming.

Genetic factors probably play a role as well, but genetic distance is often linked to physical distance and many studies do not differentiate between these two parameters. Nevertheless there is an accumulating body of evidence that a genetic relation to a patient is indeed a risk factor.

Gender and age characteristics of the contact could be important, but this has not been established firmly and the data are contradictory. BCG vaccination is partly effective against leprosy as was shown in many studies. Thus the presence of a BCG scar in a contact is likely to indicate a lower risk.

Risk factors, related to the original leprosy patient, for contact transmission are the type of leprosy and the BI.

Current evidence suggests that serological tests could be useful in defining high-risk contacts. The reviewed literature suggests that a contact who is seropositive for antibodies

against *M. leprae* has an (up to more than 20-fold) higher risk of developing leprosy.^{31,51,52} Even though the majority of seropositive contacts do not develop clinical leprosy and the majority of new cases develop out of the seronegative group, within a group of contacts of one leprosy patient, those contacts that are seropositive have an increased risk, in particular to develop MB leprosy.⁵² Presently, there are no published data relating the serological status of the patient to the risk that this patient spreads the disease. The development of a simple and relatively cheap field test for the detection of anti-PGL-I antibodies makes use of serology in field programmes feasible.⁶⁸ Other bio-molecular markers and tests could be useful in defining high risk groups among leprosy contacts as well, but these tests require either follow up visits (reactivity to lepromin) or more sophisticated laboratory facilities than those generally available in leprosy endemic areas.

The available data on leprosy justify the opinion that the stone-in-the-pond model as used in tuberculosis control could be a useful model in leprosy as well. This model is based on a concentric circle approach that assumes that the prevalence of infected individuals is highest near to the source of the infection and gradually decreases as the distance to the source increases.⁶⁹ The results of tuberculosis research strengthen the hypothesis that an effective intervention aimed at prevention of leprosy among contacts of known patients should include other contacts than household contacts and that actively looking for infected individuals elsewhere (e.g. neighbouring houses and the working place) could be effective.

From both leprosy and tuberculosis investigations, it has become clear that the bacterial load of a patient, as measured by a skin smear or a sputum smear, respectively, is an important risk factor for transmission to contacts. However, results of tuberculosis research stress the fact that the sputum status is certainly not the only risk factor. Not only contacts of MB patients but also contacts of PB patients have a higher risk of contracting leprosy than the general population. In analogy to tuberculosis, this suggests that PB patients must not be neglected as a possible source of infection, and that contact examination should also be conducted in case a patient is classified as PB.

Beyond contact tracing and examination to diagnose and treat leprosy in an early phase, other possible interventions for contacts are chemoprophylaxis and (repeated) BCG vaccination. From this review we conclude that targeted interventions should be aimed at close contacts both inside and outside the household, particularly when genetically related. Contacts of PB patients should also be included in such interventions.

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