Risk factors for developing leprosy – a population-based cohort study in Indonesia

MIRJAM I. BAKKER*, MOCHAMMAD HATTA**, AGNES KWENANG**, PETRA VAN MOSSEVELD*, WILLIAM R. FABER +, PAUL R. KLATSER* & LINDA OSKAM*

*KIT (Koninklijk Instituut voor de Tropen/Royal Tropical Institute), KIT Biomedical Research, Amsterdam, The Netherlands
**Department of Microbiology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
†Department of Dermatology, Academic Medical Center, Amsterdam, The Netherlands

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Summary  We identified risk factors associated with increased yearly incidence rates of leprosy in five island populations. Age, sex, household size and Mycobacterium leprae-specific antibodies as well as contact factors were studied. Of 94 index patients (patients diagnosed in 2000), 43 (46%) were classified as multibacillary (MB), 17 (19%) were seropositive for PGOL antibodies and 6 (7%) had M. leprae DNA in nasal swabs as determined by polymerase chain reaction (PCR) testing. All PCR positive patients were also seropositive. Forty-four of 4903 initially symptom free persons developed leprosy within 4 years, giving an incidence rate of 2·98 per 1000 person-years. Men had a 2·2 times higher risk [95% confidence interval (CI): 1·2–4·1] of developing leprosy than women. People living in households with more than 7 members had a 3·1 times higher risk (95% CI: 1·3–7·3) than households of 1–4 members. Persons who were seropositive in 2000 had a 3·8 times higher risk (95% CI: 1·1–12·6) than seronegative persons. Household contacts of MB patients had an adjusted hazard ratio (aHR) of 4·6 (95% CI: 1·6–12·9) and household contacts of PCR positive patients an aHR of 9·36 (95% CI: 2·5–34·9) compared with non-contacts. Patients with PCR positive nasal swabs, suggesting nasal excretion of M. leprae, are probably the patients with the highest transmission potential. Since all index patients who were PCR positive were also seropositive, serology seems an adequate tool to identify these patients. Preventing seropositive persons from becoming seropositive and infectious patients might break the chain of transmission.

Correspondence to: M. Bakker, KIT (Royal Tropical Institute), KIT Biomedical Research, Meibergdreef 39, 1105 AZ Amsterdam, The Netherlands (Tel: +31 20 5665450; Fax: +31 20 6971841; e-mail: m.bakker@kit.nl)
Introduction

Leprosy is still a public health problem. Even though case detection rates are not declining, vertical leprosy programmes are disappearing and disease control programs reforming. New approaches and strategies are needed which specifically address high-risk groups. Therefore, it is important to identify risk factors for developing leprosy, since this may allow rationally designed and targeted intervention strategies.

A cohort study is the best design to study risk factors for leprosy. Five population-based cohort studies have been performed after WHO introduced multi-drug treatment (MDT) in 1982.2–6 Not all cohort studies investigated the same risk factors. A large total-population study in Malawi identified household or dwelling contact as a risk factor: contacts had a 2 times higher risk compared with non-contacts. Contacts of multibacillary (MB) patients had the highest risk: 5–8 times higher compared to non-contacts.4 In the same cohort good housing conditions, education and a BCG scar was associated with a decreased risk of developing leprosy.7,8

Having specific antibodies against Mycobacterium leprae has been studied as a risk factor for leprosy in other cohort studies. Three studies failed to find a significantly increased risk among seropositive persons.5,6,9 These studies however were limited by selection and/or information bias. In a recently published cohort study of household contacts of MB patients in the Philippines with a follow-up time of 11 years, seropositive contacts had a 7 times higher risk of developing leprosy and a 24 times higher risk of developing MB leprosy.10

None of the population studies to date studied age, sex and seropositivity in addition to contact factors. The objective of this cohort study was to identify risk factors for leprosy by measuring incidence rates in the population of five islands in Indonesia during 2000–2004. Personal factors as well as contact factors were studied. Index patients were characterized by WHO classification, serology and the presence of M. leprae DNA in nasal swabs as determined by polymerase chain reaction (PCR), which has not been done in any other cohort study. The data were drawn from a population-based chemoprophylactic intervention study. The results of the intervention have been published elsewhere.11

Materials and methods

Study population and cohort

Prior to the study ethical clearance was received from the Ethical Research Committee of the Hasanuddin University and from the Ministry of Health of the Republic of Indonesia. Written communal consent was given by the community leaders each year. In June 2000, an intervention study started on five islands in the Flores Sea, Indonesia. Population and methods of this study have been described elsewhere.11 In short, rifampicin chemoprophylaxis was provided twice (in July and November 2000) to all eligible persons on the three smallest islands ( = blanket group) and to only the household and neighbour contacts of patients detected in 2000 on one other island ( = contact group). On the last island no chemoprophylaxis was provided ( = control group). All leprosy patients were treated with standard MDT directly after diagnosis.

The population of the islands was screened for leprosy during the first survey in June/July 2000 and those absent in June/July were screened in November 2000 during the second survey with coverage of 84% and 3-2%, respectively. Yearly follow-up screenings were
performed in June 2001, April 2002, April 2003 and April 2004 during the third to sixth surveys with coverage of 72%, 68%, 74% and 72%, respectively.

The present cohort includes all people, irrespective of whether they received prophylaxis or not, who did not have signs of leprosy when screened for the first time in July 2000 \( (n = 3895) \) or November 2000 \( (n = 148) \). Control group members and non-contacts of the contact group screened for the first time between 2001 and 2003 and found to be leprosy free also entered the cohort \( (n = 860) \), none of whom received prophylaxis.

OUTCOME
A population census was held before the first survey, and was updated every survey. For all surveys the same medical team performed active door-to-door screenings on all islands. Leprosy was diagnosed clinically based on detailed skin examination, including testing for anaesthesia and examination for nerve enlargement, and confirmed by an experienced medical doctor. Classification was based on the WHO system of lesion counting [paucibacillary patients (PB): 1–5 lesions, multibacillary patients (MB): >5 lesions].\(^{12}\) Classification of PB patients was later altered to MB if they had positive skin smears.\(^{13}\) Data on Ridley–Jopling classification were not collected.

PREPARATION OF MAPS
During the first survey, detailed hand-drawn maps including all houses were prepared and updated every survey. The longitudes and latitudes of approximately every fifth house were measured during the fourth survey using a hand-held Global Positioning System (GPS, Garmin, Kansas USA) and entered into Arcview 3.2 (Esri, California USA). The remaining houses were inserted into Arcview between the geo-referenced houses using the detailed maps.

CHARACTERIZATION OF THE INDEX PATIENTS
Index patients, used to determine contact status, were defined as individuals diagnosed with leprosy during their first examination in 2000. The following samples were collected to characterise the index patients: skin smears to determine the bacterial index (BI), blood to measure IgM antibodies to \( M. leprae \) PGL-1 and nasal swabs to detect \( M. leprae \) DNA. Furthermore, patients were classified according to the WHO classification system and the disability grade was measured using the standard WHO grading system (for the analyses grade 1 and grade 2 were combined).

CONTACT STATUS
Contact status was defined in two ways: (1) by the ‘traditional’ method of households, direct neighbours and next neighbours;\(^{2}\) and (2) by a ‘novel’ method of spatially defined buffers around patients using a geographic information system (GIS).\(^{14}\) Contacts were grouped according to the type of index patient based on its classification, disability grade, serological status, BI and PCR result and to the number of index patients in the household. The definition of non-contacts varied with the definition of contacts used in the different analyses. For example, when contacts are defined as only household contacts, non-contacts are all those who are not a household contact, but when contacts are defined as household and neighbour contacts, non-contacts are all those persons who are not a household or a neighbour contact.
ELISA

Blood collected from the population above 5 years old during the first survey was separated by centrifugation on the same day and the serum was kept frozen until use. The presence of IgM antibodies to *M. leprae* PGL-I was measured using an enzyme-linked immunosorbent assay (ELISA) as described previously\(^\text{15}\) using the natural trisaccharide moiety of PGL-I linked to bovine serum albumin (NT-P-BSA). Serum was diluted 1:500 and tested *in duplo* and the average value taken as final. The optical density at 450 nm (OD) of each serum was calculated by subtracting the OD value of BSA-coated wells from that of NT-P-BSA coated wells. To minimize plate-to-plate variation, the reaction was stopped when a positive reference serum reached an OD of 0.6. The cut-off value for seropositivity was set at 0.200.

PCR

Nasal specimens were collected from the index patients by gently rubbing the swab (Medical Wire and Equipment Co.), pre-wetted with saline, in one side of the nose over the lateral conchae. Each swab was directly cut and collected in a labelled tube with 0.9 ml lysis buffer (L6 buffer),\(^\text{16}\) stored at room temperature, transported to Amsterdam and stored at \(-70\)°C.

After the samples were heated for 10 min at 80°C, 95 \(\mu\)l of the supernatant was used in the DNA isolation. DNA was isolated according to Boom *et al.* (1990)\(^\text{16}\). For each sample 20 \(\mu\)l of silica coarse was used and instead of TE buffer, 50 \(\mu\)l of sterile distilled water was used for elution.

A PCR amplification for the *rlep* repetitive sequence was performed on the isolated DNA. A 2 \(\mu\)l aliquot of the isolated DNA and 1 \(\mu\)l of an internal amplification control were added to 29 \(\mu\)l of PCR mix containing 15 mM Tris-HCl pH 8.0, 50 mM KCl, 0.01% (v/v) Tween 20, 0.2 mM of each dNTP, 1.5 mM MgCl2, 1.25 units of HotGoldStar DNA polymerase (Eurogentec, Seraing, Belgium), 0.2 \(\mu\)M of primer PS3 (5’-GGA CAC GAT TAG CGC GGC GCA CGT-3’) and 0.2 \(\mu\)M of primer PS4 (5’-TTG TGG TGG GCT GGT GGG GTG TGG TGG-3’).\(^\text{17}\)

The PCR samples were incubated for 10 min at 95°C, followed by 35 cycles of 30 s denaturation at 96°C and 1 min annealing and elongation at 70°C, and a final incubation at 72°C for 1 min. Each run included negative and positive controls. Amplification reactions were visualised on a 1.2% agarose gel. Samples were positive when a PCR product with a size of 455 bp could be detected. If only the PCR product of the internal amplification control (579 bp) could be detected the sample was negative. No amplification of the internal amplification control and *rlep* product would indicate inhibition.

**Statistical Analyses**

Follow-up time was measured in person-months to adjust for the various lengths of participation. People who were leprosy free during a follow-up and had missed screening during previous follow-ups were assumed to have been leprosy free the year(s) before. The follow-up time of persons who had developed leprosy was set at the midpoint between the last screening in which they were found to be free of leprosy and the follow-up in which they were diagnosed with leprosy. The follow-up time of persons lost to follow-up was set at the midpoint between the last screening and the next possible follow-up.
The leprosy incidence rate was calculated as the number of new leprosy patients over the follow-up time and expressed per 1000 person-years. Cox proportional-hazards regression was used in the risk factor analysis. The following variables were examined: sex, age, household size (\( =\) number of people living in the house), BCG scar at intake, specific \(M. leprae\) antibodies in 2000 and contact status. Age and household size were included as time-dependent variables. Due to a high degree of collinearity some variables were analysed separately in the multivariate analysis. To adjust for the effect of the intervention on the incidence of leprosy we added a variable with four categories [control group \(n = 1568\), non-contacts of contact group \(n = 1843\), contacts of contact group \(n = 392\) and blanket group \(n = 1100\)] to all regression analyses. We tested for interaction and confounding between variables. The proportionality assumption was satisfied for all variables.

The attributable risk of each independently associated risk factor from the multivariate analysis was calculated using the following formula:

\[
\text{Population attributable risk (PAR%)} = \left[ \frac{P_{\text{exp}}(HR - 1)}{P_{\text{exp}}(HR - 1) + 1} \right] \times 100% ,
\]

with \(P_{\text{exp}} = \) total person-years exposed/(total persons-years exposed + total person-years reference category) and \(HR = \) hazard ratio of exposed versus not-exposed (= reference category).

The PAR% indicates the percentage of the total leprosy incidence that is due to the risk factor.

Results

During the first and second surveys 94 index patients were detected. Their characteristics are shown in Table 1. The MB/PB ratio was 1:1·2. The six index patients with a PCR positive nasal swab were also seropositive, all were classified as MB and three were BI positive. No inhibition was detected in the negative PCR samples. Thirteen of the 42 tested MB patients were seropositive (31%) as well as four of the 47 tested PB patients (9%). Six patients were seropositive and BI positive. Two patients, classified as MB, were positive for all four characteristics.

The cohort of 4,903 persons was studied for a total time of 177,569 person-months of observation. Of the cohort 67·4% completed follow-up. Women comprised 53·3% and the median age of the cohort was 19 years (inter quartile range: 7–35). Table 2 shows the characteristics of the study population including for each characteristic the percentage of persons with complete follow-up. The largest differences were seen for sex and age: more women (75%) than men (59%) completed follow-up and among children aged 0–5 years at entry 82% completed follow-up compared to 57% among people aged 60 or more.

In total, 44 persons developed leprosy: 7 MB leprosy, 17 PB leprosy with 2–5 lesions and 20 single lesion PB leprosy (MB/PB ratio: 1:5·3). Age at detection varied between 4 and 69 years. The overall incidence rate was 2·98 per 1000 person-years (95% CI: 2·2–4·0). Figure 1 shows the incidence rates per age group for males and females. While for men incidence rates fluctuated between different age groups, the female pattern was much more stable. For men the highest incidence rate was at age 15–19 years; in contrast, women had a reduced incidence at this age.

In bivariate analyses, the following variables were significantly related with developing leprosy: sex, household size, serological status in 2000 and contact status (see Table 3). Only household contacts had an increased risk of developing leprosy and not neighbour or buffer
contacts. Therefore Table 4 focuses on household contacts only. It shows the risk factor “household contact” grouped according to different characteristics of the index patient. Classification, BI, disability grade, serological status and PCR status of the index patient identified household contacts with an increased risk.

The number of index patients in the household seemed an important risk factor: household contacts of more than 1 patient had an increased risk of developing leprosy [hazard ratio (HR): 6·65, 95% CI: 1·46–30·3]. However, in Table 4 the combined analysis of number of index patients and PCR positivity shows that it is more important that the index patient is PCR positive than that there are multiple index patients in a household. The same holds true for the other characteristics of index patients: classification, BI, disability grade and serological status (results not shown).

Table 5 shows the results of the multivariate analyses including the population attributable risk percentage. Sex, household size, serological status in 2000 and contact status remained statistically significant. Men had a two times higher risk of developing leprosy compared to women (aHR: 2·21, 95% CI: 1·20–4·09). Persons living in households of more than seven members had a 3 times higher risk compared to households of one to four members (aHR: 3·12, 95% CI: 1·34–7·27). Persons who were seropositive in 2000 had an almost 4 times higher risk of developing leprosy compared to seronegative persons (aHR: 3·75, 95% CI: 1·12–12·6). The aHR of household contacts of PCR positive patients was 9·36

Table 1. Characteristics of the 94 index patients

|                  | n  | %   |
|------------------|----|-----|
| **Sex**          |    |     |
| Female           | 53 | 56·4|
| Male             | 41 | 43·6|
| **Age (years)**  |    |     |
| 6–14             | 17 | 18·1|
| 15–29            | 34 | 36·2|
| 30–44            | 22 | 23·4|
| 45–59            | 14 | 14·9|
| 60–73            | 7  | 7·4 |
| **Disability grade** |  |     |
| 0                | 83 | 88·3|
| 1–2              | 11 | 11·7|
| **Classification** |  |     |
| PB1              | 36 | 38·3|
| PB2–5            | 15 | 16·0|
| MB               | 43 | 45·7|
| **Bacterial index** |  |     |
| 0                | 74 | 82·2|
| 0·3–2·3          | 11 | 12·2|
| ≥3               | 5  | 5·56|
| **Serological status** |  |     |
| Seronegative     | 73 | 81·1|
| Seropositive     | 17 | 18·9|
| Not tested       | 4  |     |
| **PCR on nose swab result** |  |     |
| PCR negative     | 85 | 93·4|
| PCR positive     | 6  | 6·6 |
| Not tested       | 3  |     |
compared to non-contacts. The aHR of household contacts in general compared with non-contacts was 2·80 (95% CI: 1·09–7·22).

The increased risk of living in large households was also seen among the seronegative persons and among the non-contacts: among the seronegative persons the aHR was 2·79 (95% CI: 1·05–7·41) and among the non-contacts 2·57 (95% CI: 1·02–6·48).

The highest PAR% was found for household size (36·2% for households of 7 members), followed by sex (34·6% for males). The PAR% of seropositivity was 7·8% and for being a household contact of a MB patient it was 9·8%.

Stratified analyses for the different intervention groups (control, contact and blanket) did not show substantial differences in risk factors for developing leprosy between the groups.

**Discussion**

This study shows that household contacts of index patients with *M. leprae* DNA in their noses as determined by PCR had an almost 10 times higher risk of developing leprosy than (95% CI: 2·51–34·9) compared to non-contacts. The aHR of household contacts in general compared with non-contacts was 2·80 (95% CI: 1·09–7·22).

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**Table 2. Characteristics of the study population (4903 individuals free of leprosy at intake)**

| Characteristic                      | n   | %   | % with complete follow-up |
|-------------------------------------|-----|-----|---------------------------|
| **Time of entry in cohort**         |     |     |                           |
| Survey 1 or survey 2               | 4043| 82·5| 68·8                      |
| Survey 3, 4 or 5                   | 860 | 17·5| 60·9                      |
| **Sex**                            |     |     |                           |
| Female                             | 2611| 53·3| 75·1                      |
| Male                               | 2292| 46·7| 58·6                      |
| **Age at intake (years)**          |     |     |                           |
| 0–5                                | 982 | 20·0| 81·8                      |
| 6–14                               | 1047| 21·9| 68·2                      |
| 15–29                              | 1300| 26·5| 61·5                      |
| 30–44                              | 826 | 16·9| 63·4                      |
| 45–59                              | 448 | 9·1 | 65·2                      |
| ≥60                                | 272 | 5·5 | 56·6                      |
| **Missing**                        | 1   |     |                           |
| **Household size at intake**       |     |     |                           |
| 1–4                                | 1928| 39·3| 68·0                      |
| 5–7                                | 2250| 45·9| 65·5                      |
| 8–16                               | 725 | 14·8| 71·6                      |
| **Contact status**                 |     |     |                           |
| Non-contact                        | 4619| 94·2| 67·9                      |
| Household contact                  | 284 | 5·8 | 60·2                      |
| **BCG scar at intake**             |     |     |                           |
| No                                 | 4657| 95·1| 66·9                      |
| Yes                                | 241 | 4·9 | 78·8                      |
| **Missing**                        | 5   |     |                           |
| **Serological status 2000**        |     |     |                           |
| Seronegative                       | 3090| 97·0| 66·0                      |
| Seropositive                       | 96  | 3·0 | 68·8                      |
| **Missing ( = children < 6 years + entries after first survey)** | 1717 | 69·8 |                     |

*Non-contacts are all persons who are not a household contact of an index patient.*
non-contacts. Household contacts of patients who did not carry *M. leprae* in the nose did not have an increased risk. Also household contacts of seropositive, BI positive or MB patients had an increased risk of developing leprosy during almost 4 years follow up. Furthermore, it was shown that men had a two times higher risk than women, that living in large households increased the risk three times and that persons harbouring specific antibodies against *M. leprae* had an almost 4 times higher risk.

To our knowledge, this is at the moment the only population-based cohort that is actively being followed up annually. We used person-months to calculate incidence rates and used mid-points to calculate follow-up time. The cohort described here is part of a prophylactic intervention study. A 3-year evaluation of the intervention has shown a significant lower cumulative incidence for the blanket group compared to the control group. Since risk factors did not show substantial difference between the intervention groups, as seen in the stratified analysis, all groups were pooled together to increase the power of the study. The effect of the intervention was taken into account by adjusting for it in all regression analyses.

Contact status was based on the household status of the index patients and the cohort population during the first or second survey in 2000. The possibility of misclassification as discussed by Fine et al. (1997) also applies to our study. Contacts of patients may not have been recognised as such because their index patient had died or moved or because they had moved into a leprosy-free household prior to the first or second survey. To reduce misclassification of contact status, index patients who had moved within 6 months prior to either the first or second survey were registered as living in the house prior to the movement rather than the new house. Our contact definition was solely based on spatial grounds for which we had prepared detailed maps using GPS. Other contacts like social, work-related and familial contacts were not the focus of our study.

This study was performed in a highly endemic area for leprosy: the incidence rate was 3·0 per 1000 person-years (PY), which can be considered as high compared with incidences found in the cohort study in Northern Malawi (1·1 per 1000 PY) and the retrospective cohort study in The Philippines (1·2 per 1000 PY).
To determine the relative risk for contacts the incidence among non-contacts is used as denominator and is called the background incidence. In our study the background incidence was 2.7/1000 person-years (PY). Comparing our study results with these from four other total population cohorts indicates that the relative risk of household contacts of MB patients is increased with lower background incidences. In our study contacts of MB patients had an increased risk of 4.6 of developing leprosy compared to non-contacts. Two other studies in Burma and India found comparable relative risks for MB contacts of 4.5 and 5.0, and also had high background incidences of 5.9/1000 (annual attack rate)\(^1\) and 2.0/1000 PY.\(^2\) Two studies in the Philippines and Northern Malawi were performed in areas with lower

### Table 3. Results of bivariate Cox proportional hazard analyses of risk factors for leprosy (n = 4903)

| Time of entry in cohort | Follow up time | Cumulative no. of events | Incidence rate/1000 PY | Bivariate\(^a\) HR (95% CI) | P-value |
|------------------------|---------------|-------------------------|------------------------|-----------------------------|---------|
| Survey 1 or survey 2   | 160,685.0     | 42                      | 3.14 (2.32–4.24)       | 1.0                         |         |
| Survey 3, 4 or 5       | 16,884.0      | 2                       | 1.42 (0.36–5.68)       | 0.38 (0.09–1.61)            | 0.189   |
| **Sex**                |               |                         |                        |                             |         |
| Female                 | 99,855.8      | 17                      | 2.04 (1.27–3.29)       | 1.0                         |         |
| Male                   | 77,713.2      | 27                      | 4.17 (2.86–6.08)       | 2.01 (1.10–3.70)            | 0.024   |
| **Age (years)**        |               |                         |                        |                             |         |
| 0–5                    | 25,558.0      | 1                       | 0.47 (0.07–3.33)       | 0.13 (0.02–0.95)            | 0.045   |
| 6–14                   | 45,462.8      | 14                      | 3.70 (2.19–6.24)       | 1.0                         |         |
| 15–29                  | 47,650.8      | 14                      | 3.53 (2.09–5.95)       | 0.92 (0.44–1.94)            | 0.835   |
| 30–44                  | 31,516.0      | 10                      | 3.81 (2.05–7.08)       | 1.01 (0.45–2.28)            | 0.978   |
| 45–59                  | 16,663.8      | 3                       | 2.16 (0.70–6.70)       | 0.55 (0.16–1.92)            | 0.351   |
| ≥60                    | 10,712.8      | 2                       | 2.24 (0.56–8.96)       | 0.57 (0.13–2.52)            | 0.461   |
| **Household size**     |               |                         |                        |                             |         |
| 1–4                    | 70,143.3      | 11                      | 1.88 (1.04–3.40)       | 1.0                         |         |
| 5–7                    | 81,526.0      | 21                      | 3.09 (2.02–4.74)       | 1.71 (0.82–3.56)            | 0.149   |
| 8–16                   | 25,652.3      | 12                      | 5.61 (3.19–9.88)       | 3.47 (1.51–7.98)            | 0.003   |
| **BCG scar at intake** |               |                         |                        |                             |         |
| No                     | 16,8566.3     | 40                      | 2.85 (2.09–3.88)       | 1.0                         |         |
| Yes                    | 8896.5        | 2                       | 2.70 (0.67–10.8)       | 0.95 (0.23–3.97)            | 0.940   |
| Missing                | 106-2         | 2                       |                         |                             |         |
| **Serological status 2000** |           |                         |                        |                             |         |
| Seronegative           | 121,598.8     | 33                      | 3.26 (2.32–4.58)       | 1.0                         |         |
| Seropositive           | 3882.8        | 3                       | 9.27 (2.99–28.8)       | 3.48 (1.05–11.6)            | 0.042   |
| Missing (< = children <6 years + entries after first survey) | 52087.5       | 8                       | 1.81 (0.92–3.69)       | 0.55 (0.25–1.19)            | 0.128   |
| **Contact status**     |               |                         |                        |                             |         |
| No contact             | 120,764.0     | 29                      | 2.88 (2.00–4.15)       | 1.0                         |         |
| Neighbour 2 contact    | 21,721.8      | 6                       | 3.31 (1.49–7.38)       | 1.52 (0.50–4.59)            | 0.457   |
| Neighbour 1 contact    | 24,289.5      | 3                       | 1.48 (0.48–4.60)       | 0.72 (0.19–2.75)            | 0.634   |
| Household contact      | 10,793.8      | 6                       | 6.67 (3.00–14.9)       | 3.29 (1.11–9.77)            | 0.032   |
| No contact (> 100 m)   | 66,978.8      | 15                      | 2.69 (1.62–4.46)       | 1.0                         |         |
| Buffer contact 75–100 m| 20,566.3      | 3                       | 1.75 (0.56–5.43)       | 0.62 (0.18–2.15)            | 0.454   |
| Buffer contact 50–75 m | 23,961.5      | 8                       | 4.01 (2.00–8.01)       | 1.51 (0.64–3.56)            | 0.351   |
| Buffer contact 25–50 m | 26,683.5      | 7                       | 3.15 (1.50–6.60)       | 1.33 (0.52–3.42)            | 0.556   |
| Buffer contact 1–25 m  | 28,585.3      | 5                       | 2.10 (0.87–5.04)       | 1.15 (0.36–3.62)            | 0.814   |
| Household contacts     | 10,793.8      | 6                       | 6.67 (3.00–14.9)       | 3.57 (1.18–10.7)            | 0.024   |

PY = persons-years, HR = hazard ratio, 95% CI = 95% confidence interval.

\( ^a \)Adjusted for intervention.
background incidences of 0·82/1000 PY and 0·7/1000 PY, respectively. In the Philippines MB contacts had a RR of 7·5 and in Malawi dwelling contacts had an RR of 8. Dwelling contacts in Malawi may be more comparable to household contacts in Asia, especially in our study area where most houses consist of one or two rooms and thus most household contacts sleep together in one room. These results indicate that contact status is less important in high endemic areas. This accords with a retrospective study where in a low endemic area (Thailand) 75% of the new patients had close contact with a presumed index patient and in a high endemic area (Bangladesh) only 25%.21

The absence of increased risk among neighbour contacts may be explained by the high background incidence in our study.

Table 4. Results of bivariate Cox proportional hazard analyses to identify which household contacts have an increased risk of developing leprosy

| Follow-up time | Cumulative no. of events | Incidence rate/1000 PY | Bivariate\(^a\) HR (95% CI) | P-value |
|----------------|--------------------------|------------------------|-----------------------------|---------|
| No contact (¼ reference for all variables) | 166,775·3 | 38 | 2·73 (1·99–3·76) | 1·0 |
| Household (HH) contact | 10,793·8 | 6 | 6·67 (3·00–14·9) | 3·09 (1·20–7·94) | 0·019 |
| HH contact of 1 patient | 9111·8 | 4 | 5·27 (1·99–7·66) | 2·48 (0·83–7·40) | 0·104 |
| HH contact of >1 patient | 1682·0 | 2 | 14·3 (3·57–57·1) | 6·65 (1·46–30·3) | 0·014 |
| HH contact of PB patient | 5592·8 | 1 | 2·15 (0·30–15·2) | 1·02 (0·14–7·71) | 0·982 |
| HH contact of MB patient | 5201·0 | 5 | 11·5 (4·80–27·7) | 5·27 (1·91–14·6) | 0·001 |
| HH contact of BI negative patient\(^b\) | 9534·8 | 4 | 5·03 (1·89–13·4) | 2·40 (0·80–7·18) | 0·119 |
| HH contact of BI positive patient | 1259·0 | 2 | 19·1 (4·77–76·2) | 7·77 (1·71–35·4) | 0·008 |
| HH contact of patient without disability | 9756·5 | 4 | 4·92 (1·85–13·1) | 2·36 (0·79–7·06) | 0·124 |
| HH contact of patient with disability | 1037·3 | 2 | 23·1 (5·79–92·5) | 9·97 (2·04–48·7) | 0·004 |
| HH contact of seronegative patient\(^b\) | 8720·0 | 2 | 2·75 (0·69–11·1) | 1·33 (0·31–5·80) | 0·702 |
| HH contact of seropositive patient | 2073·8 | 4 | 23·2 (8·69–61·7) | 10·3 (3·22–33·1) | <0·001 |
| HH contact of PCR negative patient\(^b\) | 9779·5 | 3 | 3·68 (1·19–11·4) | 1·71 (0·50–5·90) | 0·394 |
| HH contact of PCR positive patient\(^c\) | 1014·3 | 3 | 35·5 (11·5–110) | 14·3 (4·17–49·3) | <0·001 |
| HH contact of 1 PCR negative patient | 7858·5 | 2 | 3·05 (0·76–12·2) | 1·40 (0·32–6·09) | 0·654 |
| HH contact of 1 PCR positive patient | 755·3 | 2 | 31·8 (7·95–127) | 13·5 (3·17–57·8) | <0·001 |
| HH contact of >1 patient, all PCR negative | 1297·5 | 1 | 9·25 (1·30–65·7) | 4·39 (0·57–33·8) | 0·156 |
| HH contact of >1 patient, at least 1 PCR positive | 259·0 | 1 | 46·3 (6·53–328) | 17·0 (1·86–156) | 0·012 |

\(^a\) Adjusted for intervention.

\(^b\) Among the contacts of patients with missing BI, serology or PCR no new patients were detected. They were grouped together with the contacts of BI negative, seronegative or PCR negative patients, respectively.

\(^c\) A PCR positive patient is a patient carrying \textit{M. leprae} in the nose as demonstrated by PCR.
Living in large households was found to be a risk factor for developing leprosy independently of contact status and seropositivity. A large household could be an indication for poverty, which could make persons more vulnerable to leprosy. A large household could also indicate cramped living conditions, which could be important for transmission.

Six index patients (6·6%) were carrying *M. leprae* in the nose as demonstrated by the *rlep* PCR. This is comparable with the results of other studies, all with a relative small sample size, using the *pra* PCR: *M. leprae* DNA in the nose was detected in 9% of the studied patients.\textsuperscript{22,23} The six index patients in our study with a positive PCR were all MB patients. The percentage of MB patients that were PCR positive in our study (6/42 = 14%) was slightly low, but falls within the range of what was found by other studies (ranged between 13–65%). These other studies were based on selected groups of MB patients.\textsuperscript{22,24–26} The demonstration of *M. leprae* DNA in the nose of leprosy patients suggests that they are excreting bacilli from the nose.

The three household contacts of PCR positive patients developed leprosy after 0·2, 1·9 and 3·3 years follow-up. As the incubation period of leprosy generally lies between 2 to 5 years, these contacts were probably already infected before June 2000. The collection of nasal swabs from patients in 2000 therefore probably marks the end of a time period in which the patient was excreting *M. leprae* from his/her nose, since after sample collection all patients received MDT.

The increased risk of developing leprosy for contacts of MB patients, BI positive patients, seropositive patients or patients excreting *M. leprae* bacteria from the nose in 2000 are strong indicators for a higher transmission potential of these patients. Disability is probably not an indicator of a higher transmission potential, but rather of a more prolonged transmission period, as disability is related to a delay in case detection.\textsuperscript{27} Since the characteristics were correlated, it is difficult to point to one characteristic as being the most important one. The relative risk of contacts of patients with a positive PCR was the highest, but the population attributable risk was highest for the contacts of MB patients. Although only a small part of the new patients were a household contact of an index patient with *M. leprae* in the nose, the increased risk among these contacts indicates that probably these infectious patients were also responsible for new incident patients by other forms of contact not studied here.

Seropositive people had an almost 4 times higher risk of developing leprosy compared with seronegative people. Several other studies did not find an increased risk among seropositive people, which could partly be due to biases such as unequal rates of loss to follow-up between seropositives and seronegatives,\textsuperscript{6,28} not using PY to calculate follow-up time,\textsuperscript{5,6} and not adjusting for co-factors such as contact status, age and sex.\textsuperscript{5,6,9} These biases do not apply to our study. A recently published study performed in the Philippines among household contacts of MB patients indicated a RR of 7·2 for seropositive contacts.\textsuperscript{10} The study in the Philippines had some methodological differences compared with our study: our follow-up time was shorter and we only measured antibody levels in 2000, while they measured antibody levels every 6 months. A person was considered positive when two successive samples were positive, increasing the specificity of their test. In our study persons who may have converted to seropositivity during follow-up were still considered as seronegative, while in the study of Douglas *et al.* the person-years of these persons counted first to the seronegative group and after seroconversion tot the seropositive group. This increased risk of seropositive persons to develop leprosy identifies a high-risk group suitable for interventions such as chemoprophylaxis.

We show that seropositivity in patients may indicate a high transmission potential. Even though the percentage of the total incidence in the population that can be identified by
seropositivity is only 7.8%, giving prophylaxis to seropositive persons may cover the most important group with regard to transmission, since they may become major sources of infection in the future. An intervention addressing seropositive persons could thus interrupt the chain of transmission and prevent the development of new patients.

Table 5. Adjusted hazard ratios of risk factors for leprosy

| Adjusteda | HR | 95% CI | P-value | PAR% |
|-----------|----|--------|---------|------|
| Sex       |    |        |         |      |
| Female    | 1.0 |        | 0.011   | 34.6 |
| Male      | 2.21 | 1.20–4.09 |         |      |
| Household size |    |        |         |      |
| 1–4       | 1.0 |        |         |      |
| 5–7       | 1.61 | 0.77–3.37 | 0.201  |      |
| 8–16      | 3.12 | 1.34–7.27 | 0.010  | 36.2 |
| Serological status 2000 |    |        |         |      |
| Seronegative | 1.0 |        |         |      |
| Seropositive | 3.75 | 1.12–12.6 | 0.032  | 7.8  |
| Missing (= children) | 0.50 | 0.23–1.10 | 0.087  |      |
| < 6 years + entries after first survey) |    |        |         |      |
| Contact status based on classification of index patient |    |        |         |      |
| No contact (= reference for all contact variables) | 1.0 |        |         |      |
| Household contact of PB patient | 0.97 | 0.13–7.32 | 0.974  |      |
| Household contact of MB patient | 4.60 | 1.65–12.9 | 0.004  | 9.8  |
| Contact status based on BI of index patient |    |        |         |      |
| Household contact of BI negative patientc | 2.13 | 0.71–6.41 | 0.178  |      |
| Household contact of BI positive patient | 8.41 | 1.76–40.2 | 0.008  | 5.3  |
| Contact status based on disability of index patients |    |        |         |      |
| Household contact of not-disabled patient | 2.18 | 0.73–6.54 | 0.165  |      |
| Household contact of disabled patient | 8.02 | 1.51–42.6 | 0.015  | 4.2  |
| Contact status based on serological status of index patient |    |        |         |      |
| Household contact of seronegative patientc | 1.28 | 0.29–5.58 | 0.746  |      |
| Household contact of seropositive patient | 7.67 | 2.33–25.3 | 0.001  | 7.6  |
| Contact status based on PCR positivity of index patient |    |        |         |      |
| Household contact of PCR negative patientd | 1.64 | 0.48–5.69 | 0.432  |      |
| Household contact of PCR positive patientd | 9.36 | 2.51–34.9 | 0.004  | 4.8  |

HR = hazard ratio, 95% CI = 95% confidence interval, PAR% = population attributable risk %.

a Adjusted for ‘each other’ plus intervention.
b Adjusted for sex, household size, serological status and intervention. The contact variables were added one at the time, because of high collinearity.
c Among the contacts of patients with missing BI, serology or PCR no new patients were detected. They were grouped together with the contacts of BI negative, seronegative or PCR negative patients, respectively.
d A PCR positive patient is a patient carrying M. leprae in the nose as demonstrated by PCR.
In conclusion, we show that in this highly endemic area for leprosy household contacts of patients with *M. leprae* DNA in the nose had the highest risk of developing leprosy. Although only small numbers of new patients were such household contact, it indicates that the transmission potential of these patients is high. Since all index patients who were PCR positive were also seropositive, serology seems an adequate tool to identify these patients. The increased risk of seropositive persons to develop leprosy offers an instrument to identify those persons who will most likely become the transmitters of leprosy and thus by preventing leprosy in this group the chain of transmission might be interrupted.

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Risk factors for developing leprosy

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Design A population based cohort study. Setting Sweden. Subjects 754 330 people born in Sweden between 1973 and 1980 and still alive and resident in Sweden at age 16 years. Our findings confirm advancing paternal age as a strong independent risk factor for schizophrenia and indicate that 15.5% of cases of schizophrenia in our cohort could be due to the patient having a father who was aged > 30 years at birth. We found a stronger association in subjects without a family history of schizophrenia, providing further evidence to support the theory that accumulating de novo mutations in the germ cells of older fathers might contribute to an increased risk of schizophrenia in their offspring. This was a population-based retrospective cohort study over 7 years (01/04/2004–31/3/2011) using electronic health records from the Clinical Practice Research Datalink linked to Hospital Episode Statistics. The study population comprised individuals with diabetes aged ≥65 years with CAP. The primary objective of this study was to determine risk factors for developing AKI within 28 days of incident CAP in patients with diabetes aged ≥65 years in England. The secondary objective was to assess whether any increased risk of AKI associated with reduced estimated glomerular filtration rate (eGFR) or proteinuria varied with age. To explore the risk factors of developing chronic pancreatitis (CP) in patients with acute pancreatitis (AP) and develop a prediction score for CP. METHODS. Using the National Health Insurance Research Database in Taiwan, we obtained large, population-based data of 5971 eligible patients diagnosed with AP from 2000 to 2013. Core tip: In this large number, nationwide population-based cohort study, we concluded that the presence of recurrent acute pancreatitis (RAP), along with alcohol consumption, age of onset, and smoking habit are 4 important risk factors of chronic pancreatitis (CP). We developed a novel prediction score model for CP with excellent discrimination and successfully validated this model in our study. @article{Bakker2006RiskFF, title={Risk factors for developing leprosy--a population-based cohort study in Indonesia.}, author={M. Bakker and M. Hatta and Agnes Kwenang and Petra Van Mosseveld and W. Faber and P. Klatser and L. Oskam}, journal={Leprosy review}, year={2006}, volume={77 1}, pages={. 48-61 } }. M. Bakker, M. Hatta, +4 authors L. Oskam. Published 2006. Medicine. Leprosy review. We identified risk factors associated with increased yearly incidence rates of leprosy in five island populations.