

## Health-Related Quality of Life amongst people affected by Erythema Nodosum Leprosum in Bangladesh: a Cross Sectional Study

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Accepted for publication 27 September 2017

### Summary

Erythema nodosum leprosum (ENL) is a multisystem reaction which affects some people with multibacillary (MB) leprosy, but more specifically those with BL or LL type leprosy. The symptoms of ENL can lead to long term physical, social and economic losses, although very little is known about the effect of ENL on quality of life. *Methods:* A cross-sectional study was conducted in northwest Bangladesh. A Bengali version of the RAND 36-Item Health Survey 1.0 (SF-36) was administered to people under treatment for ENL ( $n = 29$ ) and controls affected by MB leprosy ( $n = 46$ ) matched for: sex, treatment status, age, Disability grade at diagnosis, education level and housing type. Chi Square and Wilcoxon RST were used to analyse the data using the R statistical package.

*Results:* Patients with ENL had significantly ( $P < .001$ ) worse Health Related Quality of life (HRQoL) scores on all eight SF-36 health concepts: physical functioning, pain, role limitations due to physical and emotional limitations, emotional well-being, social functioning, energy/fatigue, and general health perceptions. Cohen's  $d$  indicated a large effect ( $d = .96$  to  $1.67$ ). The results are compared with results of other published works which examined similar populations. *Conclusion:* HRQoL is significantly impaired in Bangladeshi people suffering from ENL compared with people with MB leprosy and no ENL. ENL affects all areas of a person's HRQoL measured by the SF-36. Health care providers need to spend time addressing other aspects of a person's life and not just the physical symptoms.

## Introduction

It is recognised that leprosy may impair quality of life.<sup>1</sup> However, leprosy is a complex syndrome with diverse manifestations which may affect various people's lives differently. It would be helpful to know which features of leprosy are most important in this respect, whether the differences in health-related Quality of Life can be easily measured using a validated tool (such as SF-36), and whether the effect on quality of life is mitigated by medical treatment and other interventions.

Erythema nodosum leprosum (ENL), also called Type 2 reaction, occurs in some people affected by BL and LL type leprosy (leprosy classifications included in multibacillary (MB) leprosy). ENL has been reported to affect 4–9% of people with BL leprosy and 15–50% of people with LL.<sup>2,3</sup> ENL is diagnosed by crops of tender cutaneous or subcutaneous lesions.<sup>4</sup> However, it is a multisystem disorder and other features of the condition include severe pain, fever, oedema, neuritis, iritis, and orchitis. ENL can lead to physical disability, loss of earnings<sup>5</sup> or an inability to carry out one's normal social roles. Some people have a single acute episode of ENL which may last up to 24 weeks, while others may have chronic or recurrent episodes of ENL continuing for many years.<sup>6</sup>

Little is known about the level of impairment of quality of life attributable to ENL or how long this impairment persists. The only known study which has assessed quality of life in people with ENL is by Yap *et al.*<sup>7</sup> They used the Dermatology Life Quality Index (DLQI) to assess 48 patients with ENL and compared them to 105 smear positive MB patients without ENL. They found the patients with ENL had significantly worse DLQI scores both in the total score and in each of the domains except treatment. A limitation of the DLQI is that it does not reflect any of the extra-cutaneous features of ENL.

Several studies have assessed quality of life as it relates to leprosy: one study was done in Bangladesh,<sup>1</sup> four in South America,<sup>8–11</sup> one in Ghana<sup>12</sup> and one in India.<sup>13</sup> Most of the studies have used the WHOQOL-bref,<sup>1,8,9,11</sup> while one used an alternate version of the WHOQOL,<sup>13</sup> and one used the Short form-20 health survey assessment.<sup>12</sup> Santos<sup>9</sup> reported a correlation between increased activity limitation as assessed by the SALSA and lower quality of life. Costa<sup>8</sup> reported lower QOL scores in patients with increased pain. Tsutsumi<sup>1</sup> showed an association between reduced quality of life and increased stigma, lower education, lower income, and the presence of disability.

As part of a group of studies undertaken by the ENLIST group,<sup>14</sup> we investigated the effect of ENL on health-related quality of life (HRQoL) in people living in Bangladesh. Our hypothesis was that patients with ENL would have a worse quality of life as measured by the SF-36. We tested this hypothesis by recruiting patients with ENL and controls without ENL from a rural leprosy setting in Bangladesh and comparing HRQoL.

## Methods

We conducted a cross-sectional study, using a Bengali version of the RAND 36-Item Health Survey 1-0, administered to individuals who currently or previously suffered from ENL and to other leprosy-affected people matched for relevant criteria.

The study was carried out by Rural Health Programme (RHP), based at Nilphamari in northwest Bangladesh. RHP is a well-established programme run by The Leprosy Mission Bangladesh, providing leprosy control and treatment services as part of the National Leprosy

Control Programme for four districts with a population of 7.8 million people. Data were collected between May 2014 and August 2015.

Approval for the study was granted by the Institutional Review Board for northwest Bangladesh-TLMiB on April 22, 2014. After an explanation of the study in Bengali, eligible individuals were invited to participate and they gave written informed consent before starting the study.

The RAND 36-Item Health Survey 1.0 (SF-36)<sup>15–17</sup> was selected to assess health related Quality of Life (HRQoL) as it is a validated instrument which has been employed in the context of other chronic diseases. The SF-36 has been widely used, with citations in over 5000 publications.<sup>18</sup> A Bengali translation of the SF-36 was developed by Feroz *et al.*,<sup>19</sup> who translated and culturally adapted the SF-36 for use with patients with rheumatoid arthritis. Their study of 125 patients using the Bengali version of the SF-36 revealed good psychometric properties (Cronbach's  $\alpha > 0.78$  and test-retest reliability  $> 0.82$ ).

The SF-36 was previously translated into Bengali and validated in that form.<sup>19</sup> The Feroz *et al.*<sup>19</sup> Bengali translation of the SF-36 was back translated from Bengali to English by selected RHP staff to check for local comprehensibility. Minor changes were made in the Bengali wording of four questions as confusion arose while training the staff in administering prior version of the SF-36.

Cronbach Alpha of the final modified Bengali version of the SF-36 was calculated for each scale to confirm the consistency of items within each scale. The Cronbach Alpha ranged from .78 to .92. These values are consistent with the SF-36 reliability norms<sup>20</sup> and what was reported by Feroz.<sup>19</sup>

Study participants were selected from eleven RHP field clinics in Nilphamari and Rangpur Districts historically known to diagnose and treat more ENL cases. It was decided to only use 11 of 26 clinics in order to increase reliability with a small number of staff doing a greater number of assessments. All staff involved in the study attended a 2-day training for orientation and practice in administering the SF-36 in a reliable way.

As this field programme supports the national leprosy elimination programme, diagnosis of leprosy and of MB classification is according to national guidelines, which both follow the WHO operational criteria.<sup>4</sup> A Medical officer confirms the diagnosis in each case. Registered leprosy cases are also clinically classified by the trained field staff using Ridley Jopling criteria.<sup>21</sup> ENL was clinically defined as crops of tender cutaneous/subcutaneous lesions in a person diagnosed with leprosy. Three categories of ENL were recognised; acute ENL lasting less than 24 weeks, recurrent ENL referring to a subsequent episode beginning 28 days or more after completing anti-reaction treatment, and chronic ENL lasting more than 6 months with no treatment free interval of over 27 days.<sup>22</sup>

All patients at the selected field clinics who were newly diagnosed with ENL, or currently under treatment for ENL were requested to join the study. Following signed informed consent eligible patients were enrolled in the study, provided they were over age 15 years.

The next two people presenting at the clinic with a diagnosis of MB leprosy who did not have ENL were enrolled as control subjects, if they were willing to participate. Individuals with MB leprosy who did not have ENL were eligible for inclusion in the control group whether or not still on MDT.

Individuals in the control group were matched, as far as possible, on the following variables: a) sex, b) WHO disability grade at diagnosis, b) age, c) treatment status (under treatment with multidrug therapy or released from treatment (RFT) after completing multidrug therapy), d) educational level (literate/illiterate), and e) socio-economic level as

judged by housing type. Other variables, such as RJ classification and time since MDT diagnosis, were recorded for comparison.

All study participants were interviewed using the SF-36, at the local clinic, by a staff member trained in administering the SF-36. The SF-36 addresses eight specific health concepts, or scales: physical functioning, role limitation due to physical health problems, role limitation due to emotional problems, emotional well-being, social functioning, energy/fatigue, pain, and general health perception. This instrument is straightforward to use and appropriate for people affected by leprosy.<sup>17,23,24</sup>

Data were entered into a Microsoft Access database prepared by one of the authors, which calculated the health related concept scores. Scores were all transformed to a 0–100 scale for ease of comparison. Higher scores of the SF-36 indicate a more favourable health state. Data were imported into the R statistical package<sup>25</sup> where the graphical interface “Deducer” was used.<sup>26</sup> Data were analysed using non-parametric statistical procedures.<sup>27</sup> Data describing demographic and health status were coded as categorical variables and compared using Chi Square, while SF-36 scores were analysed using a Wilcoxon Rank Sum test. Cohen’s *d* effect size was calculated using G\*Power.<sup>28</sup>

## Results

A sample of 29 individuals with ENL and 46 MB controls participated in the study. Table 1 lists the characteristics of the two groups of subjects. There were no significant differences between the two groups, according to the selected criteria: sex, age groups, MDT treatment status, disability status, literacy, or economic status (as assessed by construction materials used in house).

The only significant difference ( $P < .001$ ) between the groups is Ridley-Jopling (RJ) classification which was not a variable preselected for matching. Table 1 shows that most of the control group was classified BT, while most of the people with ENL were classified LL.

Table 2 lists characteristics of the ENL group’s treatment and impairment. Most of the individuals with ENL had already been treated for ENL (83%) when interviewed, while the remaining 17% were newly diagnosed. The majority of those with ENL had been on treatment for less than 6 months, although one person had been treated for over 4 years. Current treatment consisted of prednisolone (41%) or prednisolone plus clofazimine (41%) while no treatment information was recorded in the remaining five cases. Finally, nerve function impairment was present in 55% of the subjects, with 10% of the nerve function impairment being recent (up to 6 months duration) and the remainder being longstanding. Amongst the ENL cases, 59% had acute ENL, 24% had recurrent ENL and 14% had chronic ENL (Table 2). No subgroup analysis was attempted in this cross-sectional study as sample size was insufficient.

Subjects with ENL had significantly lower mean HRQoL scores in all scales of the SF-36 than control subjects (Table 3). Cohen’s *d* standardised effect size is above .80 on all scales, which is typically considered a large effect. Subjects with ENL had significantly lower scores in the areas of physical functioning, pain, physical and emotional role limitations, emotional well-being, social functioning, energy/fatigue, and general health perceptions. Figure 1 compares scores on all scales for the two cohorts using box plots.

**Table 1.** Chi-Square tests of demographic and disease status in ENL cases and controls

	ENL cases ( <i>n</i> = 29)		Controls ( <i>n</i> = 46)		<i>P</i> value
	Number	Percent	Number	Percent	
Sex					0.64
Male	24	83%	36	78%	
Female	5	17%	10	22%	
Age Groups					0.11
15–30	14	48%	17	37%	
31–45	7	24%	22	48%	
≥46	8	28%	7	15%	
MDT treatment status					0.53
RFT	18	69%	35	76%	
Under treatment	8	31%	11	24%	
WHO Disability Grade					0.68
Grade 0	12	41%	22	48%	
Grade 1	11	38%	13	28%	
Grade 2	6	21%	11	24%	
Literate					0.43
Yes	13	45%	23	50%	
No	15	52%	23	50%	
Housing construction materials					0.34
Durable (tin or concrete)	18	62%	23	52%	
Semi-durable (mixed materials)	5	17%	5	11%	
Non-durable (straw/bamboo)	6	21%	16	36%	
RJ Classification					<0.001
BT	0	0%	31	68%	
BB	0	0%	1	2%	
BL	6	21%	11	24%	
LL	23	79%	2	4%	
PN	0	0%	1	2%	

## Discussion

This study demonstrates that in Bangladesh people with ENL have a lower HR-QOL as measured by the SF-36 as compared to individuals with MB leprosy with no ENL. Individuals with ENL had significantly lower HR-QOL scores in all domains compared to matched controls.

The scales showing the largest differences between those with ENL and the controls were the two role limitation domains (physical and emotional) with average scores differing by 48 and 57 points respectively. These subjects are having difficulty performing work or daily activities as a result of physical and emotional problems.

The other scales with a score change of more than 40 points were social functioning and bodily pain. Lower social functioning scores are associated with significant interference with social activities, while lower bodily pain scores are associated with severe pain which limits their engagement in life.

The clinical implications of this finding are that healthcare providers may need to spend more time addressing the needs of patients with ENL. This will take time and resources but is an important part of patient care. Since ENL can last for many months or even years, there is a need to address impairment in different aspects of the person's life (not only physical symptoms) including relationships, economic situation and mental health.

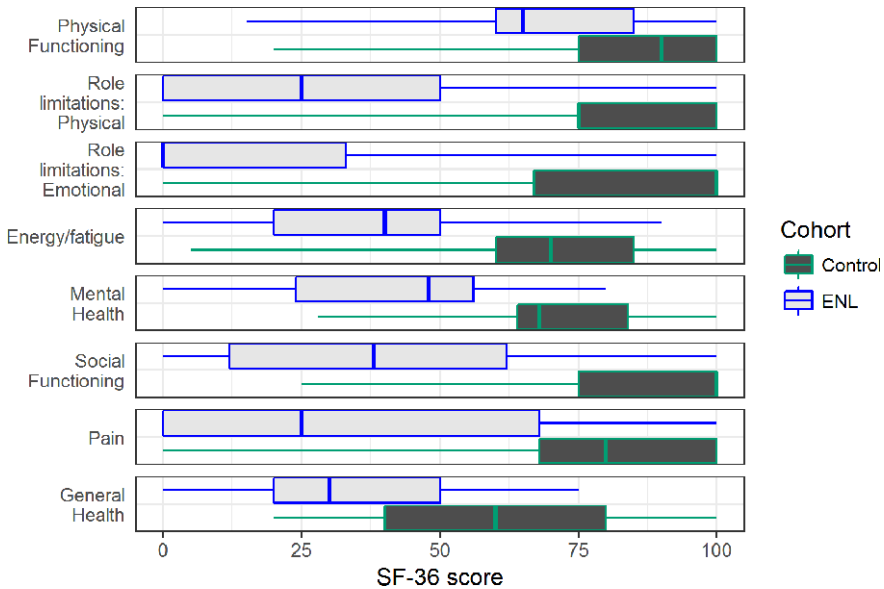
**Table 2.** Characteristics of ENL cases ( $n = 29$ )

	Count	Percent
Treatment status		
New episode	5	17%
On treatment for ENL	22	76%
Previous ENL	2	7%
Type of ENL		
Acute	17	59%
Recurrent	7	24%
Chronic	4	14%
Current treatment		
Prednisolone	12	41%
Prednisolone plus clofazimine	12	41%
Other	1	4%
Not recorded	4	14%
ENL treatment duration		
< 6 months	17	59%
6–12 months	5	17%
13–24 months	3	10%
25–36 months	1	4%
37–48 months	0	0%
49–60 months	1	3%
Not recorded	2	7%
Nerve function impairment (NFI)		
None	13	45%
Recent ( $\leq 6$ months)	3	10%
Old ( $> 6$ months)	13	45%

Figure 2 graphically compares the mean and standard deviations reported in four studies which assessed quality of life using the SF-36. The studies were collected as an exploratory review of the literature. Studies were primarily sought which used the SF-36 in the context of leprosy or a Bangladesh population, although the results of the vasculitides studies<sup>29</sup> seemed

**Table 3.** Scores on SF-36 (average/range) comparing ENL cases with other MB cases

	ENL cases			Controls			P value	Effect size d
	n	M	SD	n	M	SD		
Total score								
<i>Individual health concepts</i>								
<i>physical functioning</i>	29	65.3	24.1	46	85.6	17.7	< 0.001	0.96
<i>bodily pain</i>	29	35.7	32.3	46	78.7	22.7	< 0.001	1.54
<i>role limitations due to physical health problems</i>	29	25.0	31.3	46	73.3	32.2	< 0.001	1.52
<i>role limitations due to personal or emotional problems</i>	29	24.1	38.7	46	81.5	35.2	< 0.001	1.55
<i>emotional well-being</i>	29	41.0	22.2	46	70.7	19.3	< 0.001	1.43
<i>social functioning</i>	29	42.7	31.9	46	86.7	19.3	< 0.001	1.67
<i>energy/fatigue</i>	29	36.2	23.5	46	67.4	21.9	< 0.001	1.38
<i>general health perceptions</i>	29	35.0	20.5	46	58.0	23.4	< 0.001	1.05



**Figure 1.** Boxplot comparison of control group and ENL patients for each SF-36 scale.

germane and were included as well. The studies noted in Figure 2 are described in greater detail in the following paragraphs.

Other authors, using the SF-36, have reported reduced quality of life in individuals suffering from other chronic disabling conditions such as ENL. These would include inflammatory disorders with a fluctuating and unpredictable course, such as primary systemic vasculitis,<sup>29</sup> rheumatoid arthritis,<sup>19</sup> and lymphatic filariasis.<sup>30</sup> Koutantji<sup>29</sup> reports on vasculitides, which are similar to ENL in that they are characterised by organ damage due to multisystem inflammatory episodes which require immunosuppression. However, the population studied is from the United Kingdom, so the results are not easily compared with our study. One study<sup>19</sup> was carried out in Bangladesh amongst people with rheumatoid arthritis. They translated and validated the Bengali version of the SF 36 after overcoming issues dealing with concepts which were unfamiliar in Bangladesh. People with rheumatoid arthritis showed a low score specifically in domains of physical functioning, bodily pain and role limitations due to physical health. The findings are similar to the present study examining ENL in terms of low scores in role limitations due to physical health and pain.

Lustosa<sup>10</sup> used the SF-36 tool to assess health-related quality of life among 107 participants who were on treatment for leprosy. Analysis revealed five factors which affected quality of life: late diagnosis, MB classification, treatment for reaction (although the type of reaction was not specified), disability Grade 2 and self-reported experience of discrimination. As seen in Figure 2, the scores for all individuals in the Lustosa study were very similar to the scores found in the control group for this study. Although there was a worsening of scores for patients with Grade 2 disability or leprosy reaction in the Lustosa study, the amount of change was less than that seen in the current study. The results of this Brazilian study were similar to ours with lower scores on every scale for reaction subjects compared with controls, and the

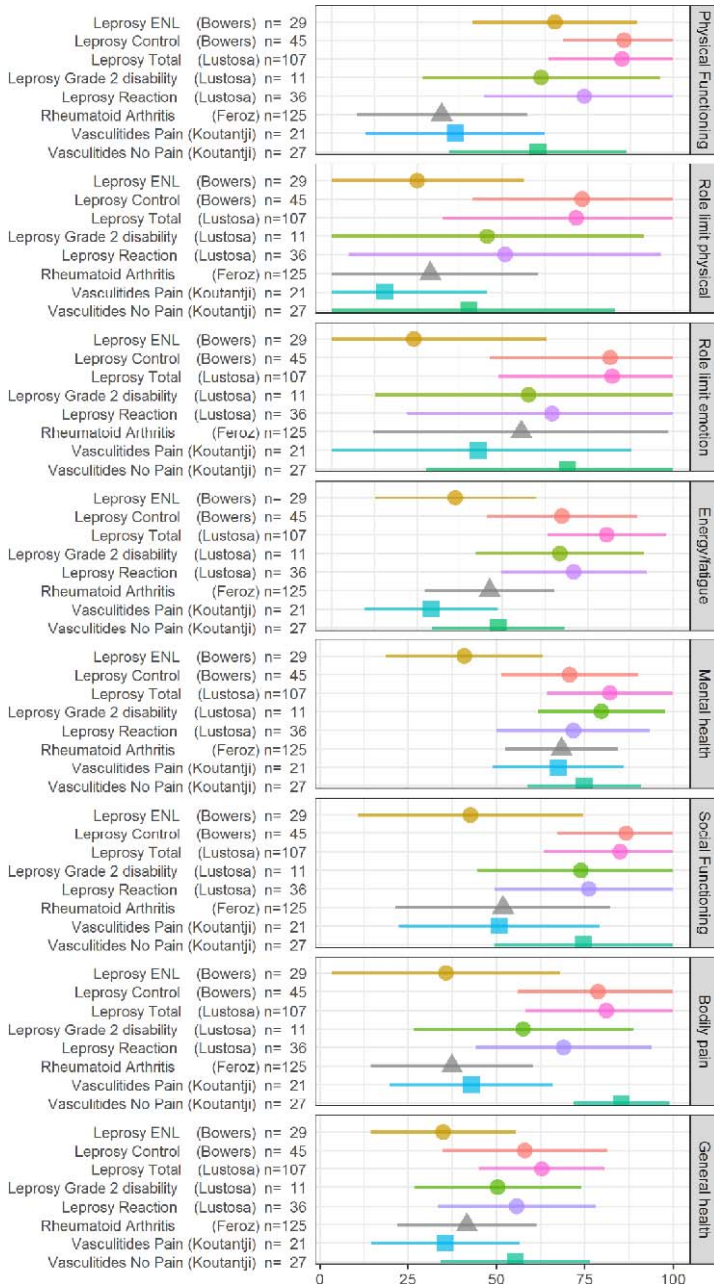


Figure 2. Comparison of the mean and standard deviation of SF-36 scores for studies mentioned in the discussion.

largest difference observed in the role limitations due to either physical functioning or emotional issues.

Comparison of quality of life assessed using different tools can be difficult. In Bangladesh, several studies assessed quality of life using the Bengali version of the World



Health Organization Quality of life (WHOQOL-bref) assessment.<sup>31–33</sup> Syed<sup>32</sup> looked at people with chronic arsenic poisoning and found significantly lower QOL scores on all WHOQOL domains for arsenic patients than for the non-patient matched controls.

Thomas<sup>34</sup> used three tools for assessing quality of life in patients with lymphatic filariasis (which causes some disabilities similar to those associated with leprosy). Their study in Kerala (India) showed that patients with *Filaria* had lower HRQoL scores than the control group using each QOL tool, although the SF-36 was not one of them.

#### LIMITATIONS OF THIS STUDY

The research design did not use RJ classification as an inclusion or exclusion criterion of the participants. It may have been difficult to find an adequate number of individuals for the control group had it been matched, but the issue was not addressed in advance. The individuals in the ENL group were predominantly LL (79%), while those in the control group were predominantly BT (67%) with only 4% having an LL classification. Smear negative BT cases are not at risk of ENL reaction, although they may suffer from Type 1 reaction and neuritis which might impair their quality of life. It is not known whether individuals with uncomplicated BL/LL may have features which would adversely, or positively, affect their HRQoL either relative to having ENL or relative to uncomplicated MB cases with BB or BT classification, or compared with MB individuals who had Type 1 reaction.

The ENL cases were not interviewed prior to the onset of ENL, so we do not know their personal baseline level of health-related Quality of life. The tool considers the respondents' condition over preceding 1 month, not just on the day of the interview. Sequential measurements of health-related Quality of Life before and during treatment and after recovery would be useful. Now that this cross-sectional study has demonstrated a sizeable impairment, planning such long-term cohort observations would be justified. The patient on treatment for ENL might have well-controlled ENL at the time of the study. Future studies should have an objective assessment of ENL severity on the day of the HRQoL assessment so that this can be incorporated into the findings.

Quality of life may be markedly influenced in some of these subjects by presence of other illnesses/disabilities, such as diabetes, as well as other socio-economic problems, and the patient's level of understanding of his/her disease. The sample size did not allow for comparisons of subgroups.

It would have been helpful to have background data on healthy members of a local population with similar socioeconomic level, such as neighbours of subjects. Background population normed scores on the SF-36, were not available for the specific regional population from which leprosy affected subjects were drawn.

#### Conclusion

Health related Quality of life is seriously impaired in Bangladeshi people suffering from ENL reaction, in comparison with people with leprosy who do not have ENL. ENL has a significant impact on all areas of a person's health-related quality of life. The areas most affected are their ability to be productive and take care of daily tasks. The adverse effect on HRQoL is of a similar order to that reported by various authors concerning leprosy-affected

people, as well as to that experienced in other chronic inflammatory or disabling disorders as reported in other studies.

Any future studies of treatment of ENL should include an assessment of change in QOL before treatment and after recovery as one of the outcome measures. It would be interesting to repeat the study using the SALSA<sup>35</sup> and P-Scale<sup>36</sup> to see if a correlation exists between SF36 domain scores and assessments of activity or participation restriction.

## Acknowledgements

This study was carried out as part of a group of studies planned by the ENLIST Group, which is a consortium of research groups interested in ENL. We acknowledge assistance from other members of the group in devising the protocol.

Rural Health Programmes is under The Leprosy Mission Bangladesh, a non-government organisation working in partnership with the Government of Bangladesh, to support the national leprosy control programme. We are grateful to field staff and authorities of The Leprosy Mission Bangladesh for facilitating this study. We are also grateful to Effect: Hope which funds the project: Leprosy Field Research in Bangladesh under RHP.

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