Childhood leprosy in a tertiary-care hospital in Delhi, India: A reappraisal in the post-elimination era

ARCHANA SINGAL, SIDHARTH SONTHALIA & DEEPIKA PANDHI

University College of Medical Sciences & GTB Hospital, (University of Delhi), Dilshad Garden, Delhi-110095, India

Accepted for publication 20 July 2011

Summary

Objective: To assess the profile and describe the clinical presentations, clinico-histopathological profile, complications and treatment compliance of childhood leprosy at a tertiary care hospital in north-east district of Delhi during 2000–2009.

Design: A retrospective institutional study of children less than 14 years of age diagnosed with leprosy and registered in a leprosy clinic during 2000–2009. Demographic, clinical, investigative and treatment data was extracted from a pre-designed proforma.

Results: A total of 1790 cases of leprosy were registered during this period, of which 172 (9·6%) were children. The majority of patients (70·3%) were more than 11 years of age with a male preponderance. History of contact was present in 25 (14·5%) patients. Borderline tuberculoid (BT) was the commonest clinical type (70·3%) followed by tuberculoid (TT) seen in 5·8%, mid-borderline (BB) in 1·2%, borderline lepromatous (BL) in 9·9%, lepromatous (LL) in 4·1%, pure neural (PNL) in 4·6% and indeterminate in 4·1% cases. More than half (52·9%) patients had a single lesion. Nerve thickening was detected in 70% cases. Slit skin smears were positive in 34 (19·8%) patients. Eighty-nine (51·7%) children were classified as multibacillary (MB) and 83 (48·3%) as paucibacillary (PB) disease by NLEP criteria. Of the available biopsy records, clinico-histological correlation was observed in 130/151 (86·1%) patients. Lepra reactions were observed in 32 patients (18·6%), Type I in 29 cases and Type II in three cases. Neuritis occurred in 11 (6·4%) and deformities in 22 (12·8%) patients. Thirty-four (19·8%) children defaulted from treatment. Two patients relapsed.

Conclusions: Despite the statistical elimination of leprosy in this region, childhood leprosy cases continue to present in alarming numbers. Our study confirmed that multibacillary disease and the complications of lepra reactions and deformities remain common in children. Early detection, treatment and contact tracing may be important in reducing the burden of leprosy in the community. There is a need to continue leprosy control activities with full vigour even in areas where, statistically, it has been eliminated.
Introduction

According to World health Organization (WHO), leprosy has been eliminated (reported prevalence less than one case per 10,000 population) from most of the 122 countries where it was considered a public health problem in 1985. However, pockets of high endemicity still persist in some regions of these countries. India achieved elimination of leprosy at national level in December 2005, although the prevalence far exceeded the elimination level in many states and union territories (UTs). By March 2009, the national prevalence was 0.72 per 10,000 with only three states/UTs lagging behind the elimination target. However, even in states/UTs that have achieved elimination, a few districts and blocks continue to have a prevalence > 1/10,000. Special plans such as Focused Leprosy Elimination Plan (FLEP) have been launched under the National Leprosy Eradication Programme (NLEP) to bring down the prevalence in these high endemic areas in India.

The profile and magnitude of leprosy in pediatric populations has an important bearing on the epidemiology of the disease and reflects the level of control in a community. A high child proportion signifies active and recent transmission of the disease, making it a robust epidemiological indicator to assess the progress of leprosy control programmes. It is expected to fall towards the elimination phase of a leprosy control programme, suggesting a decrease in transmission levels.

Material and Methods

This study was a retrospective analysis of all leprosy cases less than 14 years of age, registered at the Leprosy Clinic of Guru Teg Bahadur Hospital and associated University College of Medical Sciences, Delhi from January 2000 till December 2009. This institution is a tertiary-care teaching hospital catering to a large population of north-east district of Delhi including the native population as well as a large number of migrants from adjoining states of Uttar Pradesh, Uttarakhand, Bihar and Haryana. Cases were detected by voluntary reporting to the hospital rather than active case finding or surveys.

A case of leprosy was defined as an individual with one or more of the three cardinal signs; hypopigmented or erythematous skin lesions with definite loss or impairment of sensation, definite thickening of peripheral nerve with sensory impairment, and skin smear positive for acid fast bacilli (AFB).

Details of age, sex, state of origin, duration of symptoms, possible source of contact and clinical findings extracted from pre-designed proforma were analysed. A ‘household’ or ‘intra-familial’ contact was defined as any person in the immediate family (parents, siblings, grandparents) living in the same house and partaking in meals from a common kitchen with current or past history of leprosy. Known cases from immediate neighbourhood of the patient’s house were considered as ‘extra-familial’ contacts. Clinical details included number and distribution of lesions, pattern of nerve involvement, and complications including lepra reactions, neuritis, and deformities. The slit skin smear (SSS) results and histopathological features on skin biopsy were also evaluated. Slit skin smears were prepared from three sites – eyebrow, ear lobule and a characteristic skin lesion. The bacillary index (BI) was calculated as the mean of separate BI’s from the three sites and ranged from 0–6 + . Classification was based upon Ridley-Jopling classification and as per the criteria laid down under NLEP. As per NLEP (in collaboration with Global Alliance for leprosy elimination and WHO), the
disease is classified as multibacillary (MB) if there are six or more lesions and/or more than one nerve involvement and/or a positive skin smear from any site. Treatment given, compliance, number of defaulters and relapses were also assessed. Though many definitions have been proposed for relapse in leprosy, the one suggested by WHO (1988) states – “A patient who successfully completes an adequate course of multidrug therapy, but who subsequently develops new signs and symptoms of the disease, either during the surveillance period (2 years for PB and 5 years for MB leprosy) or thereafter”.

Results

A total of 1790 new cases of leprosy were registered during the 10-year period. Of these, 172 were children giving a 10-year average child proportion of 9·6%. Table 1 shows that the average child proportion from 2000 till 2005 (the year of elimination of leprosy in India) was 10·33% (113 children out of 1094 cases). However, in the period from 2006 till 2009 (post-elimination phase), this figure declined to 8·48% (59 children out of 696 cases).

AGE & SEX DISTRIBUTION

The majority of child patients (70·3%) were in the age group of 11–14 years, followed by 26·7% in the 6–10 years group and only 2·9% were less than 6 years of age (Table 2). The youngest patient was 2 years old. Boys outnumbered girls with a ratio of 2·3:1.

REGIONAL DISTRIBUTION

The majority of patients (62%) were children of migrants from Uttar Pradesh and Bihar, two states that have provided foci of high endemicity for many years. The remaining 38% hailed from the native resident population of Delhi state.

Table 1. Proportion of childhood leprosy cases in 10 years (Year 2000–2009)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total no. of leprosy patients</th>
<th>No. of childhood cases</th>
<th>Childhood proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>150</td>
<td>21</td>
<td>14·00</td>
</tr>
<tr>
<td>2001</td>
<td>147</td>
<td>24</td>
<td>16·33</td>
</tr>
<tr>
<td>2002</td>
<td>198</td>
<td>11</td>
<td>5·55</td>
</tr>
<tr>
<td>2003</td>
<td>217</td>
<td>26</td>
<td>11·98</td>
</tr>
<tr>
<td>2004</td>
<td>212</td>
<td>17</td>
<td>8·02</td>
</tr>
<tr>
<td>2005</td>
<td>170</td>
<td>14</td>
<td>8·23</td>
</tr>
<tr>
<td>2006</td>
<td>132</td>
<td>17</td>
<td>12·88</td>
</tr>
<tr>
<td>2007</td>
<td>134</td>
<td>13</td>
<td>9·70</td>
</tr>
<tr>
<td>2008</td>
<td>223</td>
<td>12</td>
<td>5·38</td>
</tr>
<tr>
<td>2009</td>
<td>207</td>
<td>17</td>
<td>8·21</td>
</tr>
<tr>
<td>Total</td>
<td>1790</td>
<td>172</td>
<td>9·61</td>
</tr>
</tbody>
</table>
DURATION OF DISEASE

The duration of symptoms ranged from 2 months to 5 years. In 73% the duration was under one year.

CONTACTS

Overall, 25 patients (14.5%) gave a history of contact, of which 20 (11.6%) were household contacts and only five (2.9%) were extra-familial. Amongst the contacts, the most common index patient was a parent, followed by a grandparent or a sibling and rarely a more distant relative.

CLINICAL SPECTRUM (TABLE 3)

BT leprosy was the most common type in all age groups, encountered in 70.3% patients (Figure 1).

Other clinical types were as follows: TT – 5.8%, BB – 1.2%, BL - 9.9% and LL – 4.1%. Two children with LL leprosy also had histoid lesions. PNL and indeterminate forms were seen in eight (4.6%) and seven (4.1%) patients respectively.

Table 2. Age and sex distribution of childhood leprosy patients

<table>
<thead>
<tr>
<th>Age Groups (years)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>6–10</td>
<td>31</td>
<td>15</td>
<td>46</td>
</tr>
<tr>
<td>11–14</td>
<td>85</td>
<td>36</td>
<td>121</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>52</td>
<td>172</td>
</tr>
</tbody>
</table>

Table 3. Clinical Spectrum with age distribution

<table>
<thead>
<tr>
<th>Clinical classification</th>
<th>0–5 (n)</th>
<th>0–5 (%)</th>
<th>6–10 (n)</th>
<th>6–10 (%)</th>
<th>11–14 (n)</th>
<th>11–14 (%)</th>
<th>Total (n)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>1</td>
<td>20.0</td>
<td>3</td>
<td>6.5</td>
<td>6</td>
<td>4.9</td>
<td>10</td>
<td>5.8</td>
</tr>
<tr>
<td>BT</td>
<td>3</td>
<td>60.0</td>
<td>34</td>
<td>73.9</td>
<td>84</td>
<td>69.4</td>
<td>121</td>
<td>70.3</td>
</tr>
<tr>
<td>BB</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>1.7</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>BL</td>
<td>1</td>
<td>20.0</td>
<td>3</td>
<td>6.5</td>
<td>13</td>
<td>10.7</td>
<td>17</td>
<td>9.9</td>
</tr>
<tr>
<td>LL</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>2.2</td>
<td>6</td>
<td>4.9</td>
<td>7</td>
<td>4.1</td>
</tr>
<tr>
<td>IND</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>6.5</td>
<td>4</td>
<td>3.3</td>
<td>7</td>
<td>4.1</td>
</tr>
<tr>
<td>PNL</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>4.4</td>
<td>6</td>
<td>4.9</td>
<td>8</td>
<td>4.6</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>100.0</td>
<td>46</td>
<td>100.0</td>
<td>121</td>
<td>100.0</td>
<td>172</td>
<td>100.0</td>
</tr>
</tbody>
</table>

TT = tuberculoid; BT = borderline tuberculoid; BB = mid-borderline; BL = borderline lepromatous; LL = lepromatous; IND = indeterminate; PNL = pure neural leprosy.
NUMBER AND DISTRIBUTION OF LESIONS

More than half of the patients (52.9%) presented with a single lesion. Two to five patches were detected in 13.9% and more than five patches in 28.5% cases. The distribution of patches was predominantly over the exposed parts of the body with the following order of involvement: upper extremities, face, and lower extremities. Involvement of covered parts of the body such as trunk, thighs, buttocks and proximal arms was seen in around 24% patients.

NERVE THICKENING

Around 70% children had palpable nerve thickening. Multiple nerves were thickened in 83 (48.3%) children and single nerves in 36 (20.9%). The ulnar nerve was the most commonly thickened nerve followed by radial cutaneous and common peroneal nerves.

SLIT SKIN SMEARS (TABLE 4)

SSS were positive in 34 (19.8%) children in 17 of whom the BI was 4+ or greater.

CLASSIFICATION

In this study, 89 children (51.7%) qualified for MB and remaining 83 (48.3%) for paucibacillary (PB) disease and received the corresponding WHO-recommended multi drug therapy (MDT).
Biopsy records were available for 151/172 cases including three cases of PNL where nerve biopsy was done. BT leprosy was the most common histological diagnosis. A clinico-histopathological correlation was observed in 130 out of 151 cases (86·1%) with only 21 cases demonstrating non-specific histological features.

**REACTIONS (TABLE 5)**

Reational episodes with or without neuritis occurred in 32 patients (18·6%) of which 29 (16·9%) developed Type I (reversal) reaction and three (1·7%) developed Type II reaction with lesions of erythema nodosum leprosum (ENL).

Though 19 BT patients (15·7%) contributed the highest number of reactions and neuritis, a higher rate of reaction was observed in BB (2/2 = 100%), BL (6/17 = 35·3%), and LL (3/7 = 42·9%) patients compared with BT patients (19/121 = 15·7%). Of all patients with

---

**Table 4. Slit skin smear positivity**

<table>
<thead>
<tr>
<th>Clinical classification</th>
<th>SSS Negative (BI = 0)</th>
<th>BI = 1+ to 3+</th>
<th>BI = 4+ to 6+</th>
<th>Total SSS positive cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT (n = 10)</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BT (n = 121)</td>
<td>111</td>
<td>10</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>BB (n = 2)</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>BL (n = 17)</td>
<td>0</td>
<td>6</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>LL (n = 7)</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>IND (n = 7)</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PNL (n = 8)</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total (n = 172)</td>
<td>136</td>
<td>18</td>
<td>18</td>
<td>36</td>
</tr>
</tbody>
</table>


**CLINICO-HISTOPATHOLOGICAL CORRELATION**

Biopsy records were available for 151/172 cases including three cases of PNL where nerve biopsy was done. BT leprosy was the most common histological diagnosis. A clinico-histopathological correlation was observed in 130 out of 151 cases (86·1%) with only 21 cases demonstrating non-specific histological features.

**Table 5. Lepra reactions and neuritis**

<table>
<thead>
<tr>
<th>Clinical classification</th>
<th>Type I Reaction</th>
<th>Type II Reaction</th>
<th>Percentage of patients with reaction (type I + II)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No neuritis</td>
<td>With neuritis</td>
<td>Total</td>
</tr>
<tr>
<td>BT (n = 121)</td>
<td>14</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>BB (n = 2)</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>BL (n = 17)</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>LL (n = 7)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IND (n = 7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PNL (n = 8)</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total (n = 172)</td>
<td>20</td>
<td>9</td>
<td>29</td>
</tr>
</tbody>
</table>

reversal reaction, 50% presented in reaction at the time of diagnosis and the remainder a variable time after starting MDT (Figure 2). Only one patient presented with delayed reversal reaction.

Type II reaction occurred in three patients, of whom one had BL leprosy and presented with ENL lesions at the time of diagnosis (Figure 3). The other two patients had LL leprosy and developed ENL within 6 months of MDT.

Neuritis was seen in 11 patients (6·4%), of whom nine had reversal reaction and two had ENL. Ulnar nerve was the most commonly affected nerve (9/11) with two patients developing nerve abscess. In all, 15 patients (8·7%) were given oral steroids for management of neuritis or severe reaction and 13 of them responded without recurrence. Two patients with ENL developed recurrent lesions and had to be given prolonged courses of oral steroids as well as ibuprofen and hydroxychloroquin as non-steroidal adjuvant.

DEFORMITIES

Twenty two children (12·8%) developed deformities of the hands, feet, or eyes (WHO Grade II disability), either detected at the time of diagnosis or during follow-up. Claw hand was the most common paralytic deformity seen in 10, followed by foot drop in three and facial paresis in two patients. Trophic ulceration developed in four (2·3%). One patient had collapse of the nasal bridge. Occurrence of deformities was associated with the following factors: increasing age (all deformities were seen in children more than 9 years of age), high bacillary load (80% deformities in children with MB disease with BI of 4+ or more), multiple nerve thickening, and presence of reaction at the time of presentation (in 50% cases with deformities).

Figure 2. A 13-year old boy with BL leprosy with type I reaction. Multiple erythematous, edematous and scaly plaques are visible.
TREATMENT FOLLOW-UP

The data on follow-up of the patients available till April 2010 was analysed. Out of 172 childhood cases, 138 children (80·2%) completed the recommended therapy and were released from treatment (RFT). The remaining 34 (19·8%) children defaulted while on therapy and did not report back to the institution till the follow-up period. This group included nine PB and 25 MB cases. While few of these patients may have abandoned the treatment completely, some may have migrated back to the villages in their home states to restart MDT.

RELAPSE

Disease relapse was observed in two children (one girl and one boy). Both of them had MB disease and developed features of relapse within 3–4 years of treatment completion. Old skin lesions became clinically active in both cases while new skin patches appeared in the boy who also developed foot drop. In both, relapse was confirmed with skin biopsy and MB-MDT was re-instituted for another year with good response. The boy was also given a course of oral steroids which resulted in significant improvement in foot drop.

Discussion

The proportion of children among newly detected cases of leprosy is a strong indicator of disease transmission in the community. Globally, this ratio has shown a considerable variation. As per WHO estimates in beginning of 2009, child proportion has ranged from 0·52% in Argentina to 10·14% in India to as high as 39·50% in the Federated States of Micronesia. The average 10-year child proportion of patients seen in our institution was
9.6% as against 7.06% from another tertiary care hospital of Delhi, calculated over 1997–
2002. The corresponding figures range from 4.5% in Chandigarh (1990–1999) to 9.8% in
Hyderabad in the same period. A higher rate of 31.3% has been observed in a 1990–1995
population-based survey from Tamil Nadu. A similar high incidence of childhood leprosy
(34.9% to 35.6%) has been reported in a population-based survey from rural and urban areas
of Maharashtra. The striking preponderance of cases in older children observed in our study
is not unexpected. Many previous workers have reported that majority of pediatric cases of
leprosy belong to the older age groups (5–14 years). This may be due to the relatively
long incubation period of leprosy and delayed diagnosis of indeterminate lesions in children.
While some indeterminate lesions resolve spontaneously, others progress to more definitive
forms. The higher male to female ratio of 2.3:1 is in accordance to previous Indian
studies and may be due to their greater mobility and increased opportunities for
contact. Moreover, detection in girls may possibly be lower than boys due to neglect of the
female child.

A 14.5% rate of contact in our series is lower than previous studies. While Kaur et al.
reported a contact rate of 19.7%, Jain et al. found it in 38.8% cases. Van Beers et al. have
shown that risk of a person developing leprosy is four times higher when there is a
neighbourhood contact and up to nine times higher when the contact is infranatural. Thus, it is important to
take detailed contact history and screen family members whenever possible. The study
reinforces the fact that children more often have a single lesion of leprosy. Few
authors have reported more cases with multiple lesions. Skin lesions were predominantly
seen over exposed parts of the body; a consistent observation of many previous authors.
However, up to 24% of patients had lesions over covered sites as well, emphasizing upon the
importance of thorough cutaneous examination in all children.

Though BT was the most common (70.3%) morphologic type, we detected a significant
number of older children with BL, LL and PNL. We also observed a high rate of smear
positive leprosy (19.8%) which included all patients with BB, BL and LL as well as 10 BT
patients. Smear positive leprosy is considered uncommon in childhood and has been reported
in less than 10% cases in many previous studies. Only a few studies have reported
higher smear positivity rates ranging from 17.4% to 30%. Based upon the NLEP criteria, we observed MB leprosy to be slightly more common than
PB in children. This is in contrast to most previous studies which have reported pediatric
leprosy to be predominantly paucibacillary. This difference is most likely due to the
use of a different set of criteria for disease classification by previous workers such as the 1988
or 1998 WHO classification. While the 1998 WHO classification included the number of
lesions as a criterion (not present in the 1988 classification), neither considered the number of
involved nerves as a differentiating factor. However, inclusion of the number of involved
nerves as a criterion increases the sensitivity of this classification and prevents under

treatment of many patients deserving MB-MDT. In our series too, a significant number
of patients with BT leprosy qualified for MB disease due to more than one nerve trunk
involvement.

We observed a higher rate (86.1%) of clinico-histopathological concordance as compared
to 52% reported by Sehgal and Joginder and 60.6% by Kumar et al. Kumar et al.
suggested that the non-specific histological features in childhood cases reflect the poor
immune system in children, rather than the choice of biopsy site. However, as proposed by
Nadkarni and Rege, we believe that selection of optimum lesion for biopsy might have been responsible for the high rate observed in our series.29

The high incidence of reactional episodes in 18.6%, neuritis in 9.4% and WHO Grade II deformities in 12.8% cases in our series proves that such complications are not uncommon in children. Though Jain et al. also reported high incidence of such complications (reactions – 29.7%; neuritis – 24.2%), most other workers have reported less frequent occurrence.7–10,14

We observed that occurrence of neuritis significantly increases the risk of deformities, especially in older children with MB disease. Occurrence of deformities at such a young age is truly unfortunate and the significance of careful neurological examination at the time of diagnosis and during follow-up needs to be stressed. Despite the feared adverse effects of oral steroids in children, we advocate judicious use of steroids in managing active neuritis or impending nerve paresis. Rehabilitative measures such as physiotherapy and corrective surgeries should also be offered to selected patients.

During the 10-year period, 80.2% children completed MDT on time and were released from treatment, which is slightly higher than the corresponding rate of 75% for adult patients from our institution. This may possibly be due to a relatively higher concern of the parents for treatment completion of their children. Efforts should be made to further improve treatment compliance. In our experience, many patients abandon treatment within a few months following subjective improvement in skin lesions. Migration of workers to their home states resulting in interruption or abandonment of therapy further compounds the problem. Thus, adequate counseling regarding the nature and duration of therapy should be given to parents at the first contact with the health service provider. Issue of additional kits of MDT in case of short-term migration and transferring out a patient in case of ‘permanent migration’ may rectify this problem to some extent. The concept of ‘accompanied MDT’ is another logical solution to this problem.

In conclusion, the analysis of trends of childhood leprosy from our study offers an insight into the current status of the disease in an area where leprosy has been statistically ‘eliminated’. Though a lot has been achieved at national level, much needs to be done in pockets of high prevalence in terms of case detection, patient education and counselling, in addition to MDT coverage. To sustain elimination, current leprosy control activities should be continued with full force even in a low-prevalence region like Delhi that caters to a significant number of leprosy cases who have migrated from high-prevalence regions.

References

11 Shetty VP, Thakar UH, D'souza E et al. Detection of previously undetected leprosy cases in a defined rural and urban area of Maharashtra, Western India. Lepr Rev, 2009; 80: 22–33.
16 Job CK, Baskaran B, Jayakumar J, Aschhoff M. Histopathologic evidence to show that indeterminate leprosy may be a primary lesion of the disease. Int J Lepr Other Mycobact Dis, 1997; 65: 443–449.