Relapse and deformity among 2177 leprosy patients released from treatment with MDT between 2005 and 2010 in South India: A retrospective cohort study

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Summary

Objective: To estimate the incidence of relapse among leprosy patients released after completing multi-drug therapy (MDT) during 2005–2010 under India’s National Leprosy Eradication Programme in South India.

Methods: We conducted a retrospective cohort study of leprosy patients who were released from treatment (RFT) with MDT during April 2005 and March 2010 in four purposely selected districts from South India. We clinically examined them for signs of relapse, persistence and deformity. We collected slit skin smears from those reporting signs of relapse or persistence. We computed relapse rate per 1000 person years by dividing the number of relapses by person years of follow-up and 95% confidence intervals (CI) for rates.

Findings: We tracked 3791 RFT patients and examined 58% of them. The examined and those who were not examined were similar in terms of leprosy type, year of completing MDT and gender. We identified 58 relapses (relapse rate 6·1 per 1000 person years) among the examined. Majority of these relapses occurred within 3 years post-MDT. Eighteen (31%) of the relapsed patients had deformity.

Conclusion: While low level of relapse indicates effectiveness of MDT, the burden of deformity is of concern. For maximizing treatment effectiveness and minimizing transmission, we recommend educating leprosy patients at treatment completion for self-monitoring of signs of relapse and advising them to visit nearby public health facilities or Community health workers for immediate evaluation and intervention.
Introduction

Leprosy elimination strategy focuses on treating patients with multi-drug therapy (MDT) globally, which is aimed at curing patients, preventing disabilities, reducing the reservoir of infection and thereby interrupting leprosy transmission. Relapse of leprosy is considered as a proxy indicator of effectiveness of MDT in the programme settings and is less likely to be affected by operational factors. Globally, leprosy prevention and control services are being offered as part of the general health services. Upon completion of fixed duration of MDT, the patients are labeled as released from treatment (RFT) irrespective of the prevailing clinical manifestations.

Early diagnosis of relapse and initiation of MDT are critically important to avoid undesirable complications and to prevent further transmission of leprosy infection from relapsed patients. Several studies have documented that patients who experience relapse even many years after RFT are an important source of infection for their immediate contacts. The World Health Organization (WHO) considers relapse as one of the priorities for research and WHO’s current global strategy mentions relapse as one of the main indicators for assessing the quality of anti-leprosy services. However, there is no follow-up mechanism to detect and document relapse after RFT following integration of anti-leprosy services with the general health system in the country.

In addition to relapse, occurrence of deformity after RFT is also of significant concern. Grade 2 deformities (G2D) require immediate intervention to prevent further deterioration. The global strategy for leprosy aims at reducing the rate of G2D by 35% by the end of 2015 from the base-line levels in 2010. However, information on deformity for RFT patients is also not available due to lack of follow-up data on RFT cases in the current programme setting.

In the published literature, several studies have documented relapse rates varying from 6.5 to 30.0 for PB and 2 to 80 for MB per 1000 PY. Such variability could be attributed to endemicity level in the study settings, differences in study designs, varying periods of follow-up and use of non-uniform definitions. Most of the previously reported studies were hospital-based; hence, findings from these studies may not be truly reflective of the real picture in the community. It is important to ascertain the magnitude of relapse following RFT in the integrated public health programme settings. Such information will be useful for developing strategies for effective tracking and management of relapses among RFT patients.

Indian council of Medical Research (ICMR) conducted a multi-centric study in India with the primary objective of estimating the secondary drug resistance in leprosy patients after RFT. The National Institute of Epidemiology (NIE), Chennai coordinated the South India component of the study. We analysed the data collected as part of this study to estimate the incidence of relapse among leprosy patients RFT between 2005 and 2010 under India’s National Leprosy Eradication Programme (NLEP).

Material and methods

STUDY DESIGN

This study design was that of a retrospective cohort study of leprosy patients who were declared RFT during April 2005 and March 2010.
STUDY SETTING

The study was conducted in three districts (Coimbatore, Salem and Cuddalore) of Tamil Nadu state and Chittoor district of Andhra Pradesh state in South India. These districts were selected purposely because they had an appropriate documentation of all the RFT cases during 2005 and 2010. All the four districts had varying demographic, geographic and leprosy indicators. Cuddalore reported the highest annual new case detection rate (8.18 per 100,000 population) among the study districts. Salem district reported the highest deformity rate (3.35 per 100,000 population). Although the prevalence of leprosy varied among the study districts, all of them had achieved the leprosy elimination level (< 1/10,000 population). \(^{12-15}\)

STUDY POPULATION

The study population consisted of all leprosy patients who were RFT between April 2005 and March 2010 and willing to participate in the study.

OPERATIONAL DEFINITIONS

RFT: Completion of a full course of treatment with WHO recommended MDT.

Clinical relapse: Appearance of definitive new skin lesions and/or reactivation of skin/nerve lesions with or without increase in size at any point in time after RFT.

Persisters: Those patients with active lesions, one year or more after RFT.

Type 1 reaction: Sudden onset of erythema/edema in the existing lesions or new lesions.

Type 2 reaction: Occurrence of crops of tender nodules, with or without systemic manifestations.

Grade 0 deformity: Absence of deformity.

Grade 1 deformity: Notable loss of sensation in hand or foot.

Grade 2 deformity: Visible damage or deformity.

Not traceable by address: If the data collection team or the neighbours of a potential study participant could not identify the individual in the stated address or the condition of the person was unknown.

Permanently left: A study participant who had not returned to the locality or was not likely to return in the near future.

Could not be contacted: The data collection team could verify/confirm the address of the study participant; however, the same person was not available for examination by the data collection team in more than two independent attempts during the survey period.

DATA COLLECTION

We obtained the line-list of leprosy patients who were RFT between April 2005 and March 2010 from the records of leprosy programme officials of the respective States. We trained experienced field workers to collect data. The fieldwork was undertaken between February
2012 and July 2012. Visits were attempted to residences of each patient listed in the RFT line-lists. The RFT patients were clinically examined for skin and nerve lesions and findings were recorded on body charts. We recorded information on initial grade of deformity from the RFT card and current status during our survey following thorough clinical examination of the patients to identify relapse, deformities and persistent lesions. We also collected data on education, marital status, occupation, and history of onset of clinical signs, symptoms and their duration. All the study participants with suspected clinical symptoms of leprosy relapse, reaction or persistent lesions were referred to the nearest health facility for confirmation by the medical doctors. We collected slit skin smears (SSS) from those having clinical evidence of relapse, reaction or persistent lesions. The slides were fixed and transported to NIE for smear reading. The confirmed relapse cases were treated with MDT following WHO recommended guidelines. We recorded data on reported symptoms, their duration and type and grade of deformity from the persisters.

DATA ANALYSIS

We compared the profiles of the examined patients with those who could not be examined. We computed descriptive statistics on basic profile of the cohort participants. We computed person-years (PY) of follow up as time between date of RFT and that of examination. We excluded persistent leprosy patients for calculation of relapse rate and described their characteristics separately. We estimated relapse rate per 1000 PY and their 95% confidence intervals (CI). We compared the relapse rates by gender and types of leprosy using mid-p exact test. Further, we performed multiple regression analysis using the Cox Proportional Hazard model (with district as stratification variable) to identify factors associated with relapse after RFT. We used the computed relapse rates to estimate the expected number of relapses in patients who could not be examined.

We compared the deformity status at the time of RFT with that at follow up among the patients with relapse and persistent lesions.

We used STATA 10 (StataCorp. 2007. *Stata Statistical Software: Release 10*. College Station, TX: StataCorp LP.) for data analysis.

LABORATORY ANALYSIS

The skin smear material was stained using Ziehl-Neelsen method and the bacteriological index was also recorded as per Ridley’s logarithmic scale by an experienced laboratory technician.16,17

ETHICS

This study was peer-reviewed and approved by the Institutional Human Ethics Committee (protocol ID # NIE/IEC/2011-006) of NIE. We obtained permissions from the State Leprosy Officers of Tamil Nadu and Andhra Pradesh for conducting the study. The patients were assessed after obtaining their written informed consent. We referred all the relapsed patients and those requiring further evaluation and treatment to the nearest health facilities for appropriate management.
Results

We received a line-list of 3791 leprosy patients who were RFT between April 2005 and March 2010 from the selected study settings. Of these potential study participants, 1605 (42.3%) patients were lost to follow up (LFU) due to various reasons (Figure 1). The most common reason for LFU was that the field teams could not meet 23.3% (Range: 9.7%-39%) of the study patients despite two independent visits (Figure 1).

Overall we could contact 2186 (57.7%) RFT patients and 2183 of them consented to participate. Among them 1206 (55%) were males and 41% had multi-bacillary (MB) leprosy. Forty two percent of the tracked patients had completed 3–5 years period after RFT. Among those who could not be examined \( n = 1605 \), 61% were males and 43% had MB leprosy.

We identified 53 patients with clinical relapse. Five study participants reported to have had reactions in the intervening period and we classified them as relapse cases since we could not distinguish between relapse and reactions without specific details of such events. Hence, there were 58 relapses. We removed six with persistent lesions from the denominator and hence, 2,177 (2183 – 6) RFT patients were considered for subsequent analysis (Table 1).

The median period of follow-up since RFT was 52 months (range: 23–89 months). Of all the relapses, 72% had occurred within 3 years of RFT and 95% had occurred within 5 years after RFT. Overall incidence of relapse was 6.1 per 1,000 PY (95% CI: 4.67 – 7.83) and this was observed to be higher in MB as compared to PB (7.5 vs. 5.1 per 1000 PY; \( P = 0.15 \))

Figure 1. Flow diagram describing recruitment process of the leprosy patients released from MDT in study settings: Retrospective cohort study of leprosy patients released from treatment during 2005–2010, South India.

NT – Not traceable; PL – Permanently left; CNC – Could not be contacted; PPL – Patients with persistent leprosy.
| Characteristics             | Coimbatore | Salem | Cuddalore | Andhra Pradesh, Chittoor District, India | Overall |
|----------------------------|------------|-------|-----------|-----------------------------------------|---------|
|                            | n  | N  | Rate  | n  | N  | Rate  | n  | N  | Rate  | n  | N  | Rate  |
| Age (years)                |    |    |       |    |    |       |    |    |       |    |    |       |
| ≤ 14                       | 1  | 28 | 9.88  | 1  | 31 | 8.77  | 1  | 46 | 5.30  | 0  | 47 | 0.00  |
| 15-35                      | 2  | 168| 2.71  | 7  | 181| 9.07  | 6  | 177| 7.28  | 6  | 253| 5.56  |
| 36-50                      | 2  | 110| 4.19  | 5  | 144| 7.93  | 8  | 117| 14.01 | 5  | 210| 5.69  |
| > 50                       | 2  | 189| 2.47  | 7  | 198| 8.14  | 1  | 68 | 2.80  | 4  | 210| 4.58  |
| Gender                     |    |    |       |    |    |       |    |    |       |    |    |       |
| Male                       | 5  | 260| 4.44  | 13 | 328| 9.40  | 11 | 233| 9.93  | 11 | 385| 6.91  |
| Female                     | 2  | 235| 2.00  | 7  | 226| 7.06  | 5  | 175| 6.01  | 4  | 335| 2.81  |
| Type of leprosy            |    |    |       |    |    |       |    |    |       |    |    |       |
| MB                         | 4  | 210| 4.79  | 6  | 256| 5.59  | 8  | 134| 11.75 | 11 | 302| 8.70  |
| PB                         | 3  | 285| 2.32  | 14 | 298| 10.75 | 8  | 274| 6.35  | 4  | 418| 2.29  |
| Year of release from treatment |    |    |       |    |    |       |    |    |       |    |    |       |
| 2005                       | 1  | 40 | 3.80  | 0  | 56 | 0.00  | 0  | 51 | 0.00  | 0  | 43 | 0.00  |
| 2006                       | 1  | 105| 1.63  | 4  | 105| 6.56  | 1  | 107| 1.55  | 1  | 128| 1.35  |
| 2007                       | 2  | 86 | 4.81  | 1  | 97 | 2.14  | 3  | 77 | 7.92  | 1  | 145| 1.42  |
| 2008                       | 0  | 110| 0.00  | 4  | 121| 8.75  | 1  | 70 | 3.58  | 4  | 168| 6.25  |
| 2009                       | 0  | 127| 0.00  | 11 | 138| 28.33 | 10 | 80 | 42.55 | 8  | 194| 14.56 |
| 2010                       | 3  | 27 | 51.18 | 0  | 37 | 0.00  | 1  | 23 | 19.01 | 1  | 42 | 10.91 |
| Overall                    | 7  | 495| 3.29  | 20 | 554| 8.42  | 16 | 408| 8.25  | 15 | 720| 4.98  |

Table 1. Number of relapses (n) among those examined (N) and the relapse rate per 1000 person years (PY) by selected characteristics and study settings: Retrospective cohort study of leprosy patients released from treatment during 2005–2010, South India
Men had significantly higher relapses than women (7.7 vs. 4.2 per 1000 PY; \( P = 0.03 \)). Of the four districts, Salem recorded the highest relapse rate (8.42/1,000 PY) than the remaining districts. Incidence was higher among the patients released in 2009 and 2010. We observed new lesions in 31% (\( n = 18 \)) of relapsed patients, and 59% (\( n = 34 \)) had nerve lesions (Range 1–10). The regression analysis indicated that none of the factors included in the model was significantly associated with the relapse of leprosy.

Assuming complete random missing, the expected number of relapse among patients who could not be examined (\( n = 1605 \)) would range between 32 and 55.

Of the 58 patients with relapses, 54 consented for slit skin smear collection and five (9.3%) of them were positive for \textit{M. leprae} and the duration of positivity after RFT ranged between 2.4 and 5.5 years.

Information on deformity was not uniformly recorded on RFT cards (baseline) of the 58 relapsed cases. At follow up deformities were identified in 18 (31%) patients. In case of 11 of them information on deformities at RFT (baseline) and at follow up (2–3 years) was available. Four relapsed patients developed new deformity (after RFT) and we recorded Grade 2 deformity in two of them (Table 2).

The time of occurrence of deformity could not be ascertained in seven patients due to non-availability of RFT cards.

Four of the six persistent leprosy patients were males. Their ages ranged from 29 to 63 years. The number of lesions ranged between one and nine. None of the patients with persistent leprosy was positive for \textit{M. leprae} in slit skin smear reading. Four of the persistent leprosy patients were from the MB group. All had some deformity and two presented with Grade 2 deformity.

### Discussion

The reported low relapse rate in our study has to be interpreted appropriately. During the peak of MDT campaigns, WHO reported relapse rates to be ranging between 6.5 and 30 for PB and two and 80 for MB per 1000 PY.\(^{11}\) A relapse rate of 19.7 per 1000 PY was reported in a prospective study in North India among MB patients and 19.2 among MB and 8.4 per 1000 PY among PB patients from a retrospective study in Tamil Nadu State in South India.\(^{18,19}\)

In contrast to these Indian studies, we estimated low relapse rates through retrospective cohort analysis of leprosy patients released from treatment from India’s NLEP operating

### Table 2. Deformity status at RFT and follow up: Retrospective cohort study of leprosy patients released from treatment during 2005–2010, South India

| Deformity at RFT* | Total | Grade 0 | Grade 1 | Grade 2 |
|-------------------|-------|---------|---------|---------|
| Grade 0           | 4     | –       | 2       | 2       |
| Grade 1           | 3     | –       | 3       | –       |
| Grade 2           | 4     | –       | –       | 4       |
| Total             | 11    | –       | 5       | 6       |

*In case of seven other relapsed patients, deformity status at RFT could not be ascertained due to lack of RFT cards.
within the integrated settings. Our study settings covered wide geographic areas spread over four districts in two states of India. One possibility for why the relapse rates in our study were observed to be low could be that we tracked the patients through community-based outreach and the other reports are primarily based on facility or closed cohort-based evaluation wherein patients developing some symptoms might have self-referred themselves to for healthcare. We believe that our study findings might have significant implications for the NLEP.

The low relapse rate documented in the present study suggests that the current WHO recommended MDT is effective in preventing relapses and deformities among MDT treated leprosy patients in the programme settings. It was observed that the relapse rate declined over years after RFT, and majority of the relapses occurred within 3–5 years after RFT. It is worth noting that the chance of relapse after 5 years of RFT is negligible. The relapse rate among the RFT patients in 2010 was lower than that observed among patients in 2009; this could be attributed to lower number of RFT cases, since they mostly consisted of patients who were primarily evaluated only in first three calendar months in 2010.

Among our study participants, refusals to medical examination and evaluation for evidence of relapse were negligible. Further the study participants expressed willingness to report to the health facilities for follow-up. Hence we recommend special efforts in sensitization and education of leprosy patients at RFT to identify any new lesions or other clinical events that may subsequently develop. Our study participants with relapse were willing to accept WHO MDT again. The most critical advice that they need to be given is to report to the nearby health facilities if they experience any of the signs suggestive of leprosy relapse. This approach would be very useful in management of post RFT events in the resource-limited settings wherein an active platform for periodic evaluation of RFT patients cannot be made available.

Though the overall relapse rate observed in our study was low, it is important to take a note of the following observations. Firstly, the documented relapse rate was higher among men than in women and a similar observation has been made in other studies in India. However some Indian studies have reported no significant difference in relapse rates by gender. In fact, in the multiple regression analysis we did not identify any significant risk factor for the risk of relapse in the post-RFT period.

Secondly, we identified *M. leprae* positivity through skin smears even 5 years after RFT. This documents the potential for transmission even after RFT and reiterates the need for periodic evaluation including doing skin smear testing in patients presenting with prototypic clinical signs suggesting relapses and reactions. This is particularly significant in the context of controlling the spread of leprosy to the contacts. A similar observation has been made in a study in South India.

Based on the above findings, it appears that if the RFT patients are trained to be vigilant for the first 5 years after RFT, the majority of the events of relapses may get identified early. This would provide an opportunity to prevent further complications and spread of infection through timely interventions. In addition, the national leprosy programmes must build a community-based surveillance system integrated with other services for long-term follow-up of leprosy RFT patients to timely identify relapsing cases.

The problem of deformity is particularly important among the relapsed patients as we observed almost one third of the relapsed patients with deformity and the proportion of Grade 2 deformities was observed to be high. This highlights the need for early detection and intervention for relapses among RFT patients. Grade 2 deformity observed in those patients needs immediate intervention to prevent further damage or disfigurement. Persistent leprosy was noted in few patients. It is a matter of concern and requires further evaluation.
Our study has certain limitations. About one-third of the study participants were not available for ascertainment of relapse and/or deformity. However, they were comparable to the study participants with respect to baseline characteristics. Therefore, it is reasonable to presume that the estimated relapse rates were representative of the entire RFT population in the study area.

Among those examined, the recall period was too long to accurately report the time of occurrence of new lesions. With such recall bias, some level of variation in the observed relapse rate is potentially possible. Estimates of relapses and deformity can emerge only from prospective cohort studies involving periodic evaluation of RFT cases, especially for MB leprosy with high bacterial load.\textsuperscript{22}

The absence of baseline information (at RFT) on SSS did not permit us to perform trend analysis of \textit{M. leprae} positivity in our study participants. We did not take a biopsy from the relapsed patients, which might have helped in morphological classification.

As per the protocol, if leprosy patients reported clinical symptoms such as sudden redness (showing activity in the lesion) or swelling of the lesion especially after 6 months of RFT, it is possible to distinguish between relapses and reactions by using corticosteroid intervention and evaluating remissions. We referred the patients with reactions to the nearest public health facility for appropriate management. Since long-term follow-up is beyond the scope of this study, we do not have information on steroid administration to the referred patients and response for the same. Hence, we could have misclassified some of the reactions as relapses and over-estimated the relapse rates.

Conclusions

We documented low levels of clinical relapse among leprosy patients released after completing leprosy treatment at the primary health care facilities in four districts of South India in the Government sector. However, evidence of deformity raises a concern.

Recommendations

On the basis of our study findings, we recommend that the estimates of relapses and deformities among RFT patients at the national level need to be re-examined at other settings as well. Further, despite leprosy services being administered in the integrated settings and availability of limited resources and limited skilled manpower; the RFT patients should be motivated to return for clinical evaluation for early diagnosis of relapse if they notice new skin lesions/new disabilities. There is a need to make a strategic provision for long-term follow-up of leprosy patients after RFT in the existing health systems. The patients may also be educated to voluntarily report the relapse like events to their nearest primary health facilities and Community health workers.

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Declaration

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Statement of the independence of researchers from funders

We confirm the independence of the Researchers from any Funders.

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