

## Original Research Article

# Evaluation of clinical and demographic profile of leprosy with special reference to WHO-fixed duration multidrug therapy non-responders: a cross-sectional analysis at a tertiary care centre in Maharashtra

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## ABSTRACT

**Background:** India remains one of the highest contributors to the global burden of leprosy despite declaring elimination in 2005 under National Leprosy Elimination Program (NLEP). The objective of this study was to document the clinical and socio-demographic profile of leprosy patients, determine the proportion suspected with inadequate/non-response to standard World Health Organisation (WHO)-Fixed duration multi drug therapy (FD-MDT) and identify contributory factors.

**Methods:** A cross-sectional study was conducted on 123 leprosy patients over 2 months. Screened patients were categorised into suspected MDT non-responders (Group A, 21) and those not satisfying criteria (Group B, 102) for non-responders. Medical records were abstracted and patients subjected to detailed history and clinical examination.

**Results:** Burden of WHO-MDT non-responders was 17 % (mean age 37.64 years). Majority were male in both groups. Borderline lepromatous (33%) and borderline tuberculoid (58%) were the predominant types in group A and B respectively. Among non-responders, male gender and grade 1 disability were significant associations, 17 were on extended-MDT; 1 patient was prescribed second-line drugs, 3 received both MDT and second-line drugs. More-than-half had relapsed within 5 years.

**Conclusions:** This study highlights the need for customised-treatment in selective situations to minimise relapses. Determinants in WHO-FD-MDT non-responders/relapse cases were male gender, young adults, lower socioeconomic status, lepromatous form, disability, high initial bacteriological index, non-compliance and early relapses. Leprosy eradication can be facilitated by individually focused management strategies including judicious use of bacteriological index, counseling and long-term follow-up depending on the patient profile. Active surveillance and early detection of relapse may prevent further complications and decrease drug resistance.

**Keywords:** Leprosy, Non-responders, MDT, Fixed duration, Relapse, NLEP

## INTRODUCTION

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*, mainly affecting the skin, peripheral nerves, mucosae and occasionally internal organs.<sup>1</sup>

India remains one of the highest contributors to the global burden of leprosy despite declaring elimination in 2005 under National Leprosy Elimination Program (NLEP). The fact that India continues to account for 60% of new cases reported globally each year and is among the 22 “global priority countries” that contribute 95% of world numbers of leprosy warrants a sustained effort to bring the

numbers down. In the year 2007, 137,685 new cases were detected in India, and nine years later in 2016, the number remained almost the same at 135,485, a significant increase over the 127,326 new cases detected in 2015 with 208,619 new cases in 2018.<sup>2</sup>

As on March 2018, in Maharashtra itself, 9836 new cases were recorded with Annual New Case Detection Rate (ANCDR) of 12.39 per 100000 population.<sup>3</sup>

The principle of reducing the load of infection is early diagnosis and prompt and adequate drug treatment. Correct classification and treatment of paucibacillary and multibacillary cases is a pre-requisite which reduces the chances of resistant and relapse cases. To offset the problems like resistance, relapse, and bacterial persistence, the World Health Organisation (WHO) has suggested different types of multidrug regimens which should be given in full dosages for the recommended period and without interruption.<sup>4</sup> The total number of leprosy cases registered at Sassoon General Hospitals, Pune, India (January 2018-December 2018) were 190 including 162 newly diagnosed cases. However there is paucity of data regarding the host and disease-related factors associated with continued appearance of new lesions while on or after completion of WHO/NLEP recommended fixed duration multi-drug therapy (FD-MDT) in these patients. This study aims at documenting the clinical and socio-demographic profile of leprosy patients visiting a tertiary government hospital in Pune, Maharashtra, to determine the proportion suspected to demonstrate sub-optimal response to standard WHO- Fixed duration MDT and to identify the factors associated with need for extended course of MDT and/or initiation of second-line anti-leprosy drugs.

## METHODS

This was an observational cross-sectional study conducted at BJ Medical College and Sassoon General Hospitals, Pune. The medical records of all leprosy patients registered with the leprosy care centre or attending outpatient or in-patient departments during data collection period (May to June 2019) were screened. The enrolled leprosy patients were divided into two groups A and B- Group A- patients suspected to have sub-optimal or non-response to WHO MDT and Group B- those patients who did not satisfy the criteria for non- responders. The institutional ethics committee approval was obtained. A written informed consent was taken from patients or parents/legal guardian (for patients under 18 years of age) and strict confidentiality was maintained.

### *Inclusion criteria for Group A (suspected non-responders)*

Leprosy patients prescribed extended or additional course of WHO-MDT after completion of initial fixed duration therapy (MDT2 for 6 months for PB or MDT3 for 12 months for MB). Patients on second-line drugs (Ofloxacin, Minocycline, Clarithromycin, Sparfloxacin,

Moxifloxacinetc) with or without standard WHO-MDT regimens. The operational criteria for suspected inadequate response/non-responsiveness to WHO- Fixed duration MDT regimens were as follows:<sup>5</sup>

Persistent/new lesions despite completing 6 months MDT2 or 12 months of MDT3 (after exclusion of reactional episodes) and Persistent positive or 2 log increase in the bacteriological index (BI) after  $\geq 12$  months of WHO-MDT-MB regimen.

### *Inclusion criteria for group B*

Leprosy patients not satisfying criteria for Group A and leprosy patients on first course of exclusive WHO-MDT without second-line drug. Patients whose medical records were unavailable for review, those who had not yet completed initial fixed duration course at the time of enrolment and those prescribed second-line drugs on account of intolerance to WHO-MDT were excluded from the study.

### *Tools for data collection*

Medical records of all enrolled leprosy patients were scrutinised to document patient demographics (age, gender, socioeconomic status by Modified Kuppaswamy scale (MKS), family structure), disease (type and duration of leprosy, bacteriological index, type and frequency of reactional episodes) and treatment related variables (type and duration of treatment- MDT2/MDT3/second-line drugs and any other concomitant drugs), WHO disability grades and impairment.

Information like details of any treatment interruptions and other significant co-morbidities (diabetes mellitus, TB, HIV etc) were noted on the pre-designed proforma.

Interview technique: All patients within complete medical records were subjected to detailed history and clinical examination. The data from patient proforma were verified and recorded in MS-Excel and used to analyze and correlate with potential predisposing factors for patients suspected to be non- responders for WHO-fixed duration MDT. Burden/proportion of WHO-MDT non-responders was calculated as –

$$\frac{\text{No. of leprosy patients with suspected inadequate non-response}}{\text{total number of treated leprosy patients screened}} \times 100$$

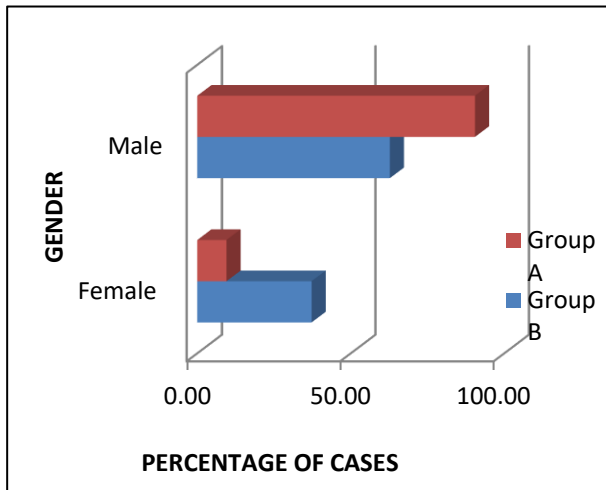
### *Statistical analysis*

The compiled data were analyzed by using percentages, mean, p-values, Chi-square test and Student t-test using Open Epi Info Statistical package program version 2.3 year 2009. Statistical significance for association of various parameters with both groups A and B and

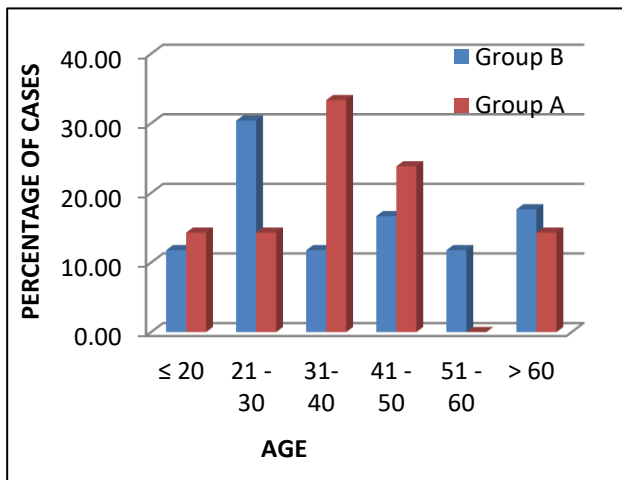
comparison between the two groups was assessed at a type 1 error rate of 0.05 ( $p < 0.05$ )

**RESULTS**

The total number of 123 leprosy patients enrolled were categorised into 2 groups: Group A (21 patients): suspected non- responders (to WHO Fixed duration MDT) and Group B (102): leprosy patients not satisfying the eligibility criteria for suspected non-responders.



**Figure 1: Gender wise distribution.**



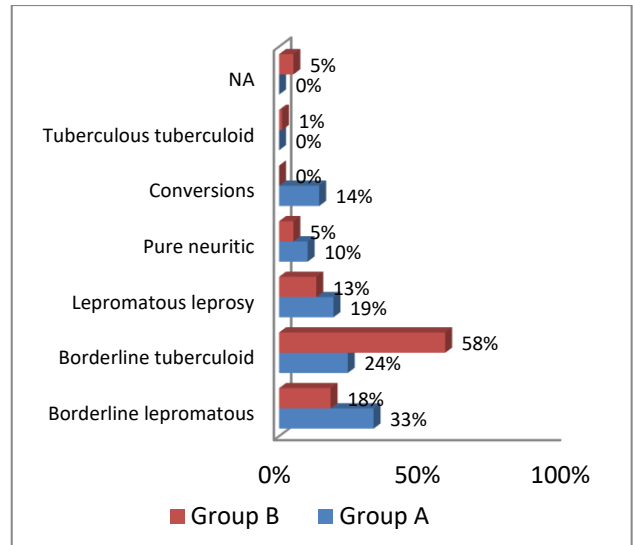
**Figure 2: Age wise distribution.**

Burden/proportion of WHO-MDT non-responders was 17%.

Figure 1 shows distribution of patients of groups A and B according to gender. Non-responders comprised 90.47% males with 9.52% females.

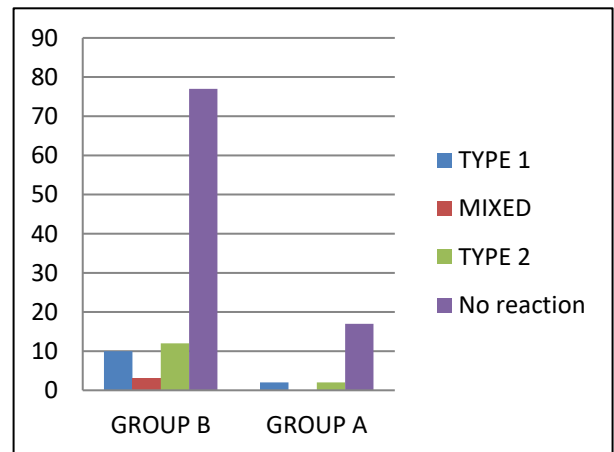
Figure 2 shows distribution of patients of groups A and B according to age at diagnosis. Mean age for group A and B was 37.67 years (standard deviation 16.74) and 39.27 years (standard deviation 16.74) respectively. In group A,

62% patients belonged to class 3, 19% class 2, 10% class 4 and 9% class 1 category of MKS scale.



\*NA=not available

**Figure 4: Distribution according to type of Lepra reaction.**

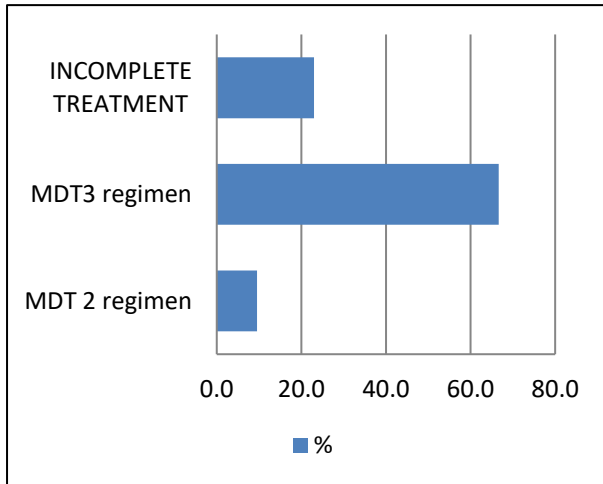


**Figure 5: Distribution of Group A patients (non-responders) according to past treatment.**

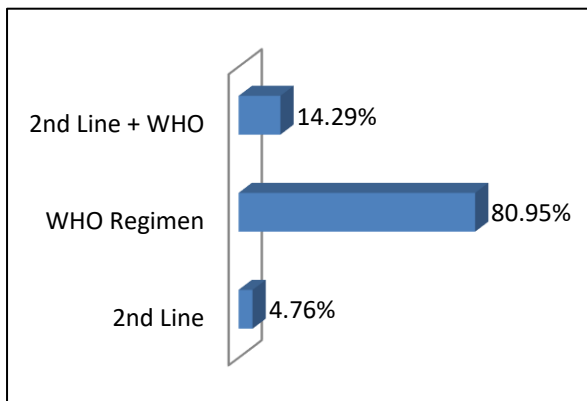
Figure 3 shows distribution of patients of group A according to type of leprosy. 33% had Borderline Lepromatous (BL); 24% borderline tuberculoid (BT); 19% lepromatous leprosy (LL); 14% showed conversions i.e. they had downgrading or upgrading along the spectrum when diagnosed with relapse (BT to LL; BT to BL); 10% had pure neuritic type. Group B constituted 58% patients of borderline tuberculoid (BT); 18% borderline lepromatous (BL); 13% lepromatous leprosy (LL), 5% with pure neuritic and 1% with tuberculous tuberculoid (TT).

Overall mean duration of disease (since initial diagnosis in case of non-responders) was 6 years with a standard deviation of 6 years in group A (range 1-29 years). Diabetes mellitus, hypertension and Human

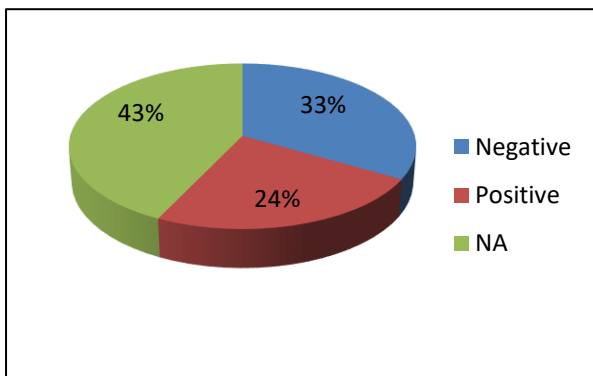
immunodeficiency virus (HIV) infection were the co-morbidities found with no statistically significant difference between the two groups.



**Figure 6: Distribution of Group A patients (non-responders) according to current treatment regimen.**



**Figure 7: Distribution of Group A (non-responders) according to bacteriological index (BI).**



**Figure 8: Frequency distribution of group A (N=21) according to BI.**

Figure 4 shows comparison between groups A and B according to type of lepra reaction. Type 1 reaction was observed in 9% of group A and 10% of group B. 12% and

9.5% patients in group A and B had type 2 reaction respectively.

**Table 1: Correlation between various parameters and Group A (non-responders).**

Parameters common for group A	P values
Gender	0.013
Type of reaction	0.858
Grade of disability	0.034
Co-morbidity (Diabetes mellitus)	0.313
Co-morbidity (Hypertension)	0.171
Co-morbidity (HIV)	0.999

**Table 2: Correlation between type of reaction and type of leprosy (Group A, non-responders).**

Type of Leprosy (N=21)	Type of reaction		
	1	2	No reaction
BL	0	0	7
BT	2	0	3
LL	0	2	2
Pure neuritic	0	0	2
Conversions	0	0	3

**Table 3: Correlation between duration of leprosy and BI in non-responders (Group A).**

Duration of Leprosy (N=12)	BI	
	Positive	Negative
≤5 years	4	5
>5 years	1	2

80% and 75% patients in group A and group B respectively did not experience any reactional episode.

3% patients in group B showed mixed type (1 and 2) of reaction.

Figure 5 shows distribution of patients in group A according to the anti-leprosy treatment received in the past. 67% had received WHO MDT3 regimen; 9.5% received WHO MDT2 regimen and 23% patients were defaulters (details not available).

Figure 6 shows distribution of group A (suspected-non-responders/relapses) according to the current treatment. 81% were prescribed extended WHO-MDT3; 14% received both second-line drugs and WHO MDT; 5% received only second-line drugs.

As depicted in Table 1, both groups showed significant association with male gender (p value 0.013) and grade 1 disability (p value: 0.034). Type 1 reaction was found to be associated with BT and BL types while type 2 was seen to be associated significantly with LL. Pure neuritic and conversion cases did not report any reactions.

Among 12 relapse cases in whom bacteriological index (BI) was available (table 2), 9 (75%) had duration under 5 years between release from treatment (RFT) and relapse. Of these, 4 (44%) demonstrated positive bacteriological index with solid bacilli (mean 3.6). Out of the remaining 3 patients with duration greater than 5 years (since RFT), 2 (66.7%) had positive BI (mean 2).

## DISCUSSION

This study enrolled a total of 123 leprosy patients from a tertiary care hospital in Pune to document the demographic, social and disease-related parameters affecting leprosy, to find out the proportion/burden of suspected WHO-MDT non-responders among the screened patients and analyse the probable factors predisposing to inadequate response.

Burden of WHO-MDT non-responders was found to be 17 % which is noteworthy. However this is an arbitrary figure as our data were collected over a short duration of 2 months and it is possible that some patients may have been missed out. Hence, it is imperative that larger studies with prospective design and longer follow-up are conducted to elucidate the accurate prevalence of non-responders and search for factors associated with poor response to WHO Fixed duration MDT. Kumar A et al assessed the cure, default, relapse and disability in a prospective cohort of 920 paucibacillary (PB) leprosy patients during follow-up of 4 years after treatment in Agra District and found incidence of relapse was 1.3/100 PY (6). Norman G et al reported on the relapses twenty years after patients were inducted into the WHO field trial and documented a relapse rate of 0.07 per 100 person years follow-up.<sup>7</sup> A Chinese study by Chen XS et al showed an overall relapse rate of 0.73/1000 patient-years among 47,276 leprosy patients.<sup>8</sup>

In our study, BL type was the most predominant sub-type among suspected non-responders with conversions from tuberculoid to lepromatous type in 14% patients pointing towards downgrading in the strength of immunity over time. Hence, most non-responder cases can be detected early if subtle skin lesions are noticed and smears examined initially as a part of surveillance. Greater caution should be exercised in providing and ensuring the completion of 12 months of WHO MDT regimen to prevent development of sub-optimal response or relapses. This observation differs from previous studies which showed all relapses were lepromatous.<sup>9</sup> A study conducted by Cellona et al found all relapses as BL or LL. Like ours, this study shows that relapses are more common in multibacillary type.<sup>9</sup> An interesting finding in our study was the occurrence of relapses even in the paucibacillary forms (BT and TT) of leprosy, indicating that these patients might need longer duration of follow-up than the current recommendation or local protocol. Also, in our study, majority of patients belonged to the borderline types with 20% of them showing reactional episodes.

In group B, borderline tuberculoid (BT) accounted for more than half (58%) which was similar to previous studies.<sup>10</sup> Lepromatous leprosy, pure neuritic leprosy and smear positivity were seen in 27.3%, 3.9% and 44.6% cases respectively in a study by Uikey et al in the Ahmedabad district of Gujarat.<sup>10</sup> Male gender and grade I disability were found to be significantly associated with sub-optimal response to WHO fixed duration therapy in our study.

Bacteriological index plays a major role in predicting the occurrence of relapse. In previous studies, it has been seen that cases with high initial B.I. are at greater risk of relapse than those with low and negative B.I.<sup>9,11</sup> In the current study, 5 relapsed patients had positive B.I, while had negative B.I. indicating that paucibacillary patients also are at risk for relapse.<sup>7</sup> However, this cannot be stated categorically as B.I was not available for 9 patients. According to current NLEP guidelines, performing baseline bacteriological index for all patients at diagnosis and again at completion of their stipulated course of MDT is no longer routinely recommended. However many leprologists believe that this investigation is a simple yet indispensable tool with diagnostic and prognostic value. For example, patients with higher initial BI can be closely monitored both clinically and bacteriologically throughout their treatment. Of these, a subset of patients might show sluggish fall in BI. Generally BI is expected to fall by 0.6 -1 log every year. It may be justifiable to prescribe extended course of MDT or even add second-line drugs in this scenario. Morphological index (MI) is another under-utilised investigation which can help keep track of potential relapses. It is the percentage of solid stained bacilli (live/viable), calculated after examining 200 red-pink staining elements, lying singly. This index indicates whether the patient's leprosy is active, responding to treatment, or whether the patient has defaulted on treatment or is developing bacterial resistance.<sup>12</sup>

Lepra reactions are acute exacerbation states due to shifts in either cell mediated immunity (Type 1) or humoral response to circulating bacillary antigens (Type 2). Any sudden erythema, edema, tenderness of the pre-existing lesion with or without a new lesion, especially during the first 6-12 months of follow-up is considered as Type 1 lepra reaction. This may be accompanied by neuritis and motor-sensory deficit and is seen in the borderline part of the spectrum (BT and BL). On the other hand, Type 2 manifests as crops of tender erythematous nodules (erythema nodosum leprosum) with constitutional symptoms. In this study, type 1 (9.5%) and Type 2 (9%) lepra reactions were found in almost similar proportion indicating that there may not be any significant association of non-responders with type of reaction whereas majority (80%) did not experience reactions. It must be emphasized that reactions are an important differential diagnosis in all leprosy patients presenting with new lesions during or after completion of treatment. They need to be ruled out with conviction before the decision is made to re-start MDT or initiate second line drugs.

For adults diagnosed with paucibacillary leprosy, the WHO currently recommends 600-mg dose of rifampin once per month and daily 100-mg doses of dapsone for 6 months. Additionally, multibacillary patients are given 300 mg monthly and 50 mg daily of clofazimine. In the current study, all patients had received initial treatment according to above guidelines. 16 out of 21 suspected non-responders had completed the specified duration of WHO-MDT regimen while 5 patients were defaulters.

Patients found to demonstrate suboptimal response to MDT were categorised as those who received MDT for extended duration and those who received second-line anti-leprosy drugs (minocycline, ofloxacin, sparfloxacin and clarithromycin). The type of regimen for relapse cases depends on 3 factors: sub-type of leprosy, previous treatment and drug resistance.<sup>6</sup> Of 21 suspected non-responders, 17 patients were on extended MDT treatment, 3 patients received both MDT and second line drugs and 1 patient was given only second-line drugs. Persisters are drug-sensitive *M. leprae* that remain dormant in immunologically protected sites and later lead to relapses. Patients with higher initial BI are presumed to have a higher proportion of persisters which may be treated successfully with extended courses of MDT. However diagnosis of resistance remains challenging and indications for second-line drugs (other than intolerance to first-line drugs) are yet to be clearly elucidated.

Leprosy is a chronic infectious disease that has a limited number of drugs available for treatment; therefore, drug resistance is likely to pose a serious impediment to its control. The key decisive factor in determining the duration of chemotherapy is the sterilizing activity of treatment measured by the relapse rate after completion of treatment. The emergence of drug resistance is a cause for concern in this regard and is a threat to any control programme for infectious diseases. The lack of prioritization in research and also of resources, and the absence of information on the magnitude of drug resistance, cannot be considered as evidence that drug resistance does not exist in leprosy. It is generally believed that a combination of more than two drugs, with different mechanisms of action, taken regularly for a sufficient period, will prevent the emergence of drug resistance. Resistance to rifampicin and dapsone is reported. Clofazimine and minocycline resistance have not yet been reported.<sup>13</sup>

The period of time between diagnosis of leprosy to detection of suspected non-responder status is important in determination of factors responsible for relapse. When analysed in the present study, 12 out of 21 (57%) were diagnosed as relapse within five years of first diagnosis while six patients had relapse after five years. This indicates that although most patients had early-onset relapses, few patients can present with late onset lesions, thereby underlining the importance of continued clinical and microbiological surveillance after treatment discontinuation.

Many significant findings were observed which could predict the occurrence of relapse and direct more group-specific treatment and active surveillance. Factors found to be associated with relapse were younger age, male gender, joint family and lower socioeconomic status and BL type of leprosy. We found three adolescent patients which highlights the importance of vigilant screening of school children particularly in leprosy endemic areas. Overcrowding and poor economic status may impair compliance and contribute to relapses and re-infection. Eleven patients in class 4 MKS scale belonged to nuclear families showing that overcrowding may not be the sole factor affecting relapse rates, economic status has a major effect attributable to poor health-care seeking behaviour and less time available due to semi-skilled type of occupation.

Our study found that BI and time of presentation with new lesions plays an important role dictating individualised treatment strategy and duration of post-treatment follow-up to minimise further complications. This is consistent with a study by Cellona et al where among 181 patients with high average pre-MDT BIs ( $\geq 4+$ ), there were 11 relapses, equalling a cumulative risk of 10.1% at 16 years after MDT. This justifies the need for long-term follow up, extended MDT for patients with high initial BI and counselling.<sup>9</sup>

The strength of our study is that an attempt was made to seek factors associated with WHO MDT non-responders in post-elimination era. Also, a wide range of variables were assessed for socio-demographic profile of leprosy. Most previous studies have focused on individual factors like bacteriological index, type of leprosy and reaction, socioeconomic status or family structure, while association between various factors has not been detailed hitherto. The limitation of our study is the small sample size of suspected non-responders as only patients attending our health care facility within a short period of data collection were recruited.

## CONCLUSION

This study reiterated that leprosy and its relapse continue to be a concern even a decade after elimination in India. The overall patient profile revealed male predominance, with a predilection for lower socio-economic classes and younger population. Multibacillary forms were more common than paucibacillary. Determinants found in WHO Fixed duration (FD) MDT non-responders/relapse cases were male gender, young adults, lower socioeconomic status, lepromatous form, disability, reactional episodes, high initial bacteriological index, non-compliant patients and early relapses. Although the effectiveness of FD MDT has been established through its role in the elimination of leprosy with good acceptability by patients and public health-care administrators worldwide, this study highlights the need for customised treatment in selected cases to prevent relapses. Since the current burden of leprosy is considerably lower than a decade ago, it is possible to

redirect efforts towards eradication by a focused treatment plan including counselling and long-term surveillance. Socio-economic upliftment and increased awareness among health care providers and community would go a long way towards achievement of the elusive goal of leprosy eradication.

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