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Original Article

Estimation of Deleterious Events in 577 Leprosy Patients Released from Treatment Between 2005-2010 in Urban and Rural Areas of Maharashtra

VP Shetty[1], SS Pandya[2], SM Kamble[3], S Shah[4], AR Dighe[5], VV Pai[6], UH Thakar[7]

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This is a study of deleterious events in leprosy patients released from treatment (RFT) between 2005-2010, in 3 municipal health posts in Mumbai (SA1 urban) and 5 primary health centres (Gavan, Apta, Nere, Wavanje and Ajivali) in Panvel Taluka (SA2 Rural) of Raigad district of Maharashtra. There were a total of 1162 registered RFT patients including 542 in SA1 and 620 in SA2 of which a total of 577 including 350 MB and 227 PB patients were successfully traced and examined in 3 annual home visits between 2012-2014. Remaining 588 (51%) were either lost to follow-up or non-consenting. The sampling conditions for both SA1 and SA2 in the context of markers such as MB : PB ratio, were found to be satisfactory. Total of 104 (18%) cases were detected with deleterious events. Five were children (4.8%). Females out-numbered males (M: F=0.8:1). The proportions were similar in SA1 (16%) and SA2 (19%). It was higher in MB (SA1=20%, SA2=15%) as compared to PB patients (SA1=11.7, SA2=8.3%). Neuritis was the most common event (64 patients), followed by relapse (54 patients), the majority being BT-BB treated with 12 months MB-MDT. Other events were, persistence of skin lesion in 31, silently progressing neuropathy in 13, lepra reaction in 21 cases. Simultaneous deleterious events were seen in 60, recurrent neuritis/reaction in 27, and worsening nerve function impairment (NFI) in 52 patients. While rates/frequencies of different deleterious events may not be truly representative of magnitude of these problems in this patient population due to significant loss to follow-up and different durations of follow up, these figures highlight the need for a vigorous Post-RFT surveillance, timely and appropriate management of deleterious events.

Key words : Leprosy, Post RFT, deleterious event, relapse, estimation

[1] VP Shetty*, Senior Scientist
[2] S Pandya, Research Officer
[3] SM Kamble, Research Assistant
[4] S Shah, Public Health Research
[5] AR Dighe, Research Assistant
The Foundation for Medical Research, 84-A, RG Thadani Marg, Worli, Mumbai-400018, India.
[6] VV Pai, Director, Bombay Leprosy Project, VidnyanBhavan, VN Purav Marg, Sion, Chunabhatti, Mumbai-400022, India.
E-mail: bombayleprosy@gmail.com
[7] UH Thakar, Secretary, Kustha Rog Nivaran Samiti, Shantivan, PO - Nere, Taluka - Panvel, District - Raigad, India
E-mail: hknsnational@yahoo.co.in
***Corresponding author:** Dr Vanaja P Shetty **e-mail:** fmr@fmrindia.org, fmrmum@gmail.com

Introduction

Under the National Leprosy Eradication Programme (NLEP), newly diagnosed patients are treated with Multidrug therapy (MDT) for 12 months of a 3-drug combination for Multibacillary (MB) cases, and for 6 months of a 2-drug combination for Paucibacillary (PB) cases (NLEP). In order to facilitate compliance with treatment, the blister pack is delivered to the patient's home by the local health worker (generally ASHA worker). Maharashtra has reported a treatment completion rate of 97.2% (NLEP progress report 2013-2014).

Deleterious events such as neuritis, reactions, silently progressing neuropathy and most importantly disease relapse are known to occur in treated patients (Ali et al 2005, Beck-Bleumink 1992, Shetty et al 2005). The State's public health services have paid scant attention to active follow-up and timely detection and treatment of such events. This makes it difficult to assess post-MDT situation and the efficacy of the treatment regime and the programme.

A three-year multicentric study was conducted in India under the aegis of and funded by the Indian Council of Medical Research (ICMR) with 2 main objectives, *viz.,* (A). Estimation of post treatment deleterious events and relapse in particular under Primary Health Care facility and B) to determine the level of drug resistance in relapse and new cases in the area under study. Four centres that participated in these aspects of the study were: The Foundation for Medical Research (FMR), Mumbai; National Institute for Epidemiology (NIE-ICMR), Chennai; Father Muller Medical College (FMMC), Mangalore; Blue Peter Health Research Centre (BPHRC), Hyderabad.

In line with the agreed upon protocol, FMR included patients Released From Treatment (RFT) between 2005 and 2010 from 3 Health Posts (HP) in Mumbai (Urban) and 5 Primary Health Centres (PHCs) in Panvel block in Raigad district (Rural). The data collected from PHC/HP records (no= 1165), followed by tracing, direct interviews, clinical and neurological examination of available and consenting RFT patients (no=577). Those detected with deleterious events during study period of 3 years (no=104) were further laboratory investigated. The findings were analysed; a) to estimate the deleterious events in the urban and rural settings. b) The information was further compared with the baseline and other data entered in the PHC record to study the differences.

Ethical Considerations

The study received ethical clearance from the Foundation's Ethics Committee (IEC No: FMR/IEC/LEP/02/2011). All ethical requirements, interrogations and investigations for undertaking the study were strictly followed and informed consent obtained. Permissions were obtained from State and Local Body Health officials, including for consulting HP and PHC records.

Study Area, Subjects and Methods

Urban (SA1): G-North, G-South and H Municipal Wards in Mumbai, served by respective 'Health Posts'. Health Post (HP) is the urban counterpart of Primary Health centre and serves a population of about 50,000.

Rural (SA2): Panvel Taluka in Raigad district served by 5 Primary Health Centres (PHCs) *viz* Gavan, Apta, Nere, Wavanje and Ajivali.

Primary Health Centre (PHC): represents the second tier of the three-tier rural public health care system in India and serves a population of 20,000-30,000 as per the norms of the Ministry of Health and Family Welfare.

The two locations one rural and one urban were selected in view of the long association with FMR research projects, and FMR staff's familiarity with the terrain (Shetty et al 2009, 2013). Most

importantly they had been categorised as "high endemic" areas (NLEP 2013-14).

Inclusion/eligibility criteria

Patients registered by public health authorities in the two study areas, and recorded as having completed the course of WHO-MDT in the period 1st April 2005 - 31st March 2010 (eligible cases); those who were available and agreeable to examination and investigations (examined cases) (Table 1).

Definitions:

All definitions except neuropathic are, as per the WHO SEA-GLP-2009. 4 operational guidelines. Following definitions were used:

(i) **Recurrence of Lesion/s: Reappearance** and reactivation of old skin lesion with/ without increase in size or new Nerve Function Impairment (NFI).

(ii) **Relapse:** Re-occurrence of the disease at any time after the completion of a full course of MDT, or increase in Bacteriological Index (BI) by two logs or more from a site on the skin as compared to BI from the same site at a previous examination.

(iii) **Poor responder:** Below-standard/less than standard decline in BI i.e., < 1 log /per year or persistence of well-defined, clinically active, anaesthetic lesions, one year or more after RFT.

(iv) **Type 1 Reaction (T1R):** Acute onset appearance of erythema/oedema in existing skin lesions or appearance of new lesions, in Borderline Tuberculoid (BT) to Borderline Lepromatous (BL) spectrum of the disease. Oedema of the hands, feet and face may be seen.

(v) **Type 2 Reaction (T2R):** Acute, sub-acute or recurring appearance of crops of tender nodules with or without neuritis, fever with or without other systemic manifestations (myositis, arthritis, synovitis, orchitis etc}, in BL and LL spectrum of the disease.

(vi) **Neuritis:** Pain/tenderness in one or more nerves.

(vii) **Silent Neuropathy:** Progressive or new nerve function impairment (NFI) not accompanied by pain or tenderness.

(viii) **Nerve Function Impairment:** Sensory impairment/s only in the area of supply of named peripheral nerve, detected using graded monofilaments (Grade 1 deformity). Motor loss also present on voluntary muscle testing, MRC Scale, (Grade 2 deformity). (Bell - Kortoski and Tomancik 1987, Brandsma 2000)

(ix) **Neuropathic pain:** Pain caused by a lesion or disease of the Somato - sensory system (Haanpaa et al 2004).

Data Collection: Listing, base line clinical and treatment details of patients registered and shown as released from treatment (RFT) between 1st April 2005 and 31st March 2010, was obtained from the registers maintained at the respective HP and PHCs. SA1 provided 542 and SA2 provided 620 RFT cases. Baseline data at registration as well as during treatment, of the entire eligible cases (No=1162) from HP/PHC was copied into structured data collection forms. This included name, age, gender, address, clinical and treatment details, information about reaction and its management, and deformity status.

Examined Cases No=577 included 171 in SA1 and 406 in SA2 areas (Table 1)

Time-Table of Examinations, First Visit (EX-1) and two annual follow-ups (EX-2 and EX-3) are as follows:

In SA1: EX-1 completed by October 2012; EX-2 completed by October 2013; and EX-3 completed

by May 2014.

In SA2: EX-1 completed by April 2012; EX-2 completed by July 2013; and EX-3 completed by March 2014.

At EX-1, a total of 577 RFT patients including 171 from SA1 and 406 from SA2 were questioned in detail on disease history, treatment compliance; about any new events or persisting lesions/ problems (skin and/or nerve); on their view about the treatment. Social and personal details such as marital, educational and employment status, and history of house hold contact were also enquired into. They were then examined clinically. Those with single evidence of deleterious events as defined above were advised to attend FMR's weekly clinic for further lab investigations, treatment and management.

At EX-2 and EX-3, all the 577 patients were re-examined in the following 2 years to identify those with continuing/worsening or new events. Enquiries were also made about therapeutic interventions in the previous year.

Collection of Samples for Laboratory Investigations:

Slit Skin Smear (SSS): Obtained from 3-4 sites, in 57 patients with events or suspected to have relapsed. Smears were heat fixed and stained with Ziehl-Neelsen and examined for acid fast bacilli -AFB (Ridley 1955).

Skin Biopsy: Obtained under local anaesthesia from the edge of an active or a newly developed lesion in 34 cases. Others did not consent for a biopsy. The specimen was divided into 3 pieces and processed for (a) histopathology b) mouse foot-pad assay (c) in 'RNA Later'® for molecular biological studies.

(a) Histopathology: Specimens were fixed in Formol-Zenker, processed for light microscopy and sections were stained with Fite-Faraco for acid fast bacilli (AFB). The Ridley-Jopling scale was used for the classification of the disease (Ridley and Jopling 1966).

(b) & (c) Details and results of the Mouse Foot-pad assay and Molecular biology studies will be published separately.

Statistical Methods: Data entry was done in MS Excel. Quantitative analysis was performed using SPSS version 19. Only the patients who were clinically examined in the 3 consecutive years were included in 'examined'. The 'eligible' and 'examined' in SA1 and SA2 study areas were further compared for sampling conditions with regard to gender proportion and treatment (MB/PB) groups (Table 2). Findings in the “examined” group in SA-1 and SA-2 study area were analysed separately and collectively with respect to;

1) Personal details, clinical classification, frequency and grade of deformity and type of post-RFT event;
2) A Comparison with corresponding data from HP/PHC records;
3) Sociodemographic features and history of contact with leprosy-affected person in the family.
4) Other laboratory findings in “Patients with events”.

Results

In SA1 urban component, 171/542 (32%) of RFT cases were examined. In SA2 (rural) the number examined were 406/620 (65%) of RFT cases. Total numbers of RFT cases examined were 577, comprising 350 (61%) MB and 227 (39%) PB cases (Table 2). Others (51%) were either lost to follow up or non consenting. In both SA1 and SA2 examined and eligible cohort compared well with each with respect to proportion of MB and PB cases thus satisfying the sampling conditions to some extent (Table 2).

Table 1 : Eligible and 'examined' (cohort under study) in the two study areas i.e. Mumbai (SA1) and Panvel (SA2)

Study Area	#Eligible	#Contacted	#Examined
SA1	542	542	171 (32%)
SA2	620	620	406(65%)
Total	1162	1162	577 (50%)

Table 2 : Gender vs Treatment groups of eligible cases (n=1162) and 'examined' cases (n=577)

	Eligible (%)			Examined (%)		
	SA1=542	SA2=620	Total=1162	SA1=171	SA2=406	Total=577
Male	409(75)	349(56)	758(65)	108(63)	222(55)	330(57)
Female	133(25)	272(44)	404(35)	63(37)	184(45)	247(43)
Ratio	3:1	1.2:1	1.8:1	1.7:1	1.2:1	1.3:1
Rx group						
MB	349(65)	351(57)	700(60)	113(66)	237(58)	350(61)
PB	193(36)	269(43)	462(40)	58(34)	169(42)	227(39)
Ratio	1.8:1	1.3:1	1.5:1	1.9:1	1.4:1	1.5:1

Table 3 : Reasons for Lost to Follow-up

	Reasons for Lost to Follow-up	SA1	SA2
1	Refused consent	16	9
2	Not traceable/ wrong address	231	121
3	Home or slum area demolished/left area permanently	114	70
4	Died	10	17
	Total	371(68%)	217(35%)

Patients lost to follow-up and reasons: In SA1 and SA2 68% and 35% of RFT patients respectively were lost to follow-up. The chief reasons were inability to trace the patient due to wrong address (SA1=42%; SA2=19%); patient having "left area permanently" (SA1=21%; SA2=11%). Number recorded as died was lower in SA1 (1.8%) than SA2 (3%) (Table 3).

Socio-Demographic Features: Illiteracy was lower in urban patients (SA1=23%; SA2=43%) 77% of urban patients and 51% of rural patients were gainfully employed. There was no difference in marital status (SA1=67%; SA2=66%) and in number of disease-affected per age group in urban and rural patients. It was also noted that the majority of RFT patients were in age group 15-50 years (SA1=75%; SA2=78%).

Clinical Findings and Treatment Compliance History - a Comparison with HP/PHC Record in the examined patients: In ~50% of HP and PHC registers no entries had been made for number of nerve and skin lesions, presence of nerve

Table 4 : Year wise detection of "Patients with events" number & (%)

	Examined 1		Examined 2		Examined 3		
	SA1 (n= 171)	SA2 (n= 406)	SA1 (n= 171)	SA2 (n= 406)	SA1 (n= 171)	SA2 (n= 406)	Total (n=577)
Events	20 (12)	50 (12)	7 (4)	14 (3.7)	1	12 (3)	104 (18)

Table 5 : Cumulative Occurrence of "Patients with events" for 3 years in SA1 and SA2

"Patients with events"	SA1 (%)	SA2 (%)	Total (%)
No	143 (84)	330 (81)	473 (82)
Yes	28 (16.4)	76 (18.7)	104 (18.6)
Total	171	406	577

Table 6 : Occurrence of "Patients with events" in MB and PB treatment groups

	No. with events / No. examined & (%)		
Treatment group	SA 1	SA 2	Total (%)
MB	22/113 (19)	49/237 (21)	71/350 (20)
PB	6/58 (10)	27/169 (16)	33/227 (15)
MB:PB	1.9:1	1.3:1	1.3:1

Table 7 : "Patients with Events" in relation to gender in 'examined' cases

	SA 1	SA 2	Total (%)
	No. with events / No. examined & (%)		
Male	15/108 (14)	40/222 (18)	55/330 (17)
Female	13/63 (20)	36/184 (21)	49/247 (20)
M: F	0.7 : 1	0.8 : 1	0.8 : 1
MB - Male	10/108 (9)	31/222 (14)	41/330 (12)
PB - Male	5/108 (5)	9/222 (4)	14/330 (4)
Ratio	2 : 1	3.4 : 1	2.9 : 1
MB - Female	9/63 (14)	21/184 (11)	30/247 (12)
PB - Female	4/63 (6)	15/184 (8)	19/247 (8)
Ratio	2.2 : 1	1.4 : 1	1.5 : 1

enlargement/involvement and Lepra-reaction. By contrast, this was not the case with regard to deformity Grade, where entries were made in > 95% of cases. Proportion of MB cases was higher in SA1 (MB: PB=1.9:1) as compared to SA2 (MB:PB=1.3:1) (Table 2).

Treatment Compliance: In SA1 area, 2/171 (1%) and in SA2 area 56/406 (14%) of the “examined”, admitted to having dropped out of the treatment for reasons such as , a) Mistaking a Lepra-reaction for drug side-effects (20/58), b) Disappearance of the lesion/felt better (12/58), c) Child patients

Table 8 : Relapse occurrence in MB and PB cases (SA1 and SA2 combined)

	MB (%)	PB (%)	Total (%)
Relapse including Rx drop outs (n=62)	41/350 (11.7)	21/227 (9.2)	62/577 (11.1)
Relapses, excluding the Rx dropouts (n=54)	37/316 (11.7)	17/204 (8.3)	54/520(10.4)

Table 9 : Occurrence of different category of events among 'examined' and Cases with events (SA1 & SA2 combined)

Category of events	Total no of RFT patients 'examined' in study N=577	
	No. detected with events/ total no. 'examined' & (%)	
Total no. detected with events over 3 years	104/577	(18)
Multiple events	62/577	(10.7)
Neuritis	64/577	(11)
Relapse (excluding Rx dropouts)	54/ 519	(10.4)
T1R	23/577	(3.6)
T2R	3/577	(0.7)
Persistence of active lesions	31/577	(5.4)
Silently progressing neuropathy	13/577	(2.2)
Number with Neuropathic pain	2/577	(0.4)
Neuritis cases receiving steroids in the past	18/65	(28)
Relapse Cases receiving steroids in the past	16/54	(29.6)
Recurring reaction and/or neuritis in the past	27/104	(26)
Relapse second time	2/54	(3.7)
Had TB as co-morbidity in the past	2/104	(2)
Detection of Nerve function impairments(G1+G2) at examination	52/104	(50)

refusing to swallow tablets (4/58), d) Drugs not delivered by ASHA worker (10/58), e) Skin turning dark (12/58).

Post-RFT deleterious Events: Total of 104 Patients (104/577=18%), were detected with events, 70 during the 1st round of examination (EX-1), 21 during the second round (EX-2) and 13 during the 3rd round (EX-3) of examination (Table 4). Five among them were children (below age 14 =4.8%). More than one event ("Multiple events") were seen in 62/104 (60%). Proportion of patients seen with events were similar in the 2 study areas; (SA1=28/171 (16.3%); SA2=76/406 (18.7%)) (p=0.554) (Table 5). In the examined subjects of SA1 area the MB: PB ratio was 1.9: 1, in SA2 area same ratio was 1.3: 1 and overall MB: PB ratio was also 1.3: 1 (Table 6). Among the patients detected with events, Male to female ratio was 0.8:1; Contrasted with "Eligible" it was 1.8:1; and in "examined" the ratio was 1.3:1 (Tables 7 and 2).

Occurrence of events in relation to MB/ PB group and gender: In SA1 and SA2 combined 71/350 (20%) of MB and 33/227 (15%) of PB patients were seen with events. (Table 6) Proportion of MB

cases with events was higher in males (MB: PB= 2.9:1) as compared to females (MB: PB=1.5:1). There were 55 PB cases recorded with 'Single Skin Lesion" (SSL) at baseline, 7 had events (7/55= 13%). Notably all were from SA2 study area.

Relapses among those who Completed Treatment and Treatment Drop-outs: Of 62 relapse cases recorded, 8 including 4 MB and 4 PB cases, were in treatment drop outs (8/58). Thus total number relapsed cases after complete treatment stand at 54/520 (10.4%) compared with 8/58 (13.7%) in drop-outs. The frequency of relapse in MB group was 11.7% and 8.3% in PB (p=0.2) (Table 8).

Event Type and its frequency: With regard to event type Neuritis was seen in 64, Relapse in 62 Persistence of Lesions in 31, Reaction in 26, Silently progressing neuropathy was seen in 13 cases. Symptoms suggestive of neuropathic pain were seen in 2 cases (Table 9).

Recurrent Lepra Reaction/Neuritis: During EX-1, EX-2 and EX-3 it was found that; Recurrent Post-RFT event/s occurred such as: T1R=13/104 (12.5%), T2R=4/104 (3.8%), Neuritis=10/104 (9.6%). These patients had sought and received treatment (chiefly corticosteroids) from: Leprosy NGO: 15/27 (56%); Private Practitioners: 4/27 (15%), HP/PHC: 5/27 (19%) while details were not available in 3 cases. 18/64 (28%) with recurrent neuritis and 16/62 (26%) with relapse had received cortico steroids during MDT. Two MB patients with relapse had received a second course of MB-MDT for recurrence of lesions. Two patients (2/104) gave a history of treatment for pulmonary TB (Table 9).

Change in Classification on Re-examination: On re-examination of 104 patients with post-RFT deleterious events, there was change in 9/28 in SA1 urban area and 24/76 in SA2 rural settings (Table 10). In SA1 area 2/28 (PB who should have got MB treatment) got less than desired treatment whereas this number was 10/76 in SA2 area. No impact of this could be related with adverse events.

Table 10 : Change in Classification (WHO) 'At baseline' and 'At examination'

Study area	Class - At baseline (PHC)	Class- On Examination	
		MB	PB
SA1	MB = 22	17	5
	PB = 6	2	4
SA 2	MB = 49	42	7
	PB = 27	10	17

Table 11 : Post RFT events in relation to "Incubation Time" (i.e. Duration between RFT and detection with events)

	No. with events / no. of cases 'examined' in that time period	
Incubation Time	Events (%)	Relapse (%)
1-3 years	20/84(24)	9/84(11)
3-5 years	46/217(21)	29/217(13.4)
5-7 years	28/207(14)	19/207(9.3)
7-9 years	10/72(19)	5/72(7)

Table 12 : Frequency of Nerve Function Impairment (NFI) among eligible, 'examined' and "Patients with event/s" in SA1 and SA2

Groups	NFI at base line (PHC Record)			NFI at examination (Interview Record)		
	SA1 (%)	SA2 (%)	Total (%)	SA1 (%)	SA2 (%)	Total (%)
Eligible=1162 (%) with NFI	148/542 (27)	52/620 (8)	200/1162 (17)			
'Examined'=577 (%) with NFI	61/171 (36)	33/406 (8)	94/577 (16)	57/171 (33)	84/406 (21)	141/577 (24)
'Examined' (excluding cases with events)=473 (%) with NFI	48/143 (34)	25/ 330 (8)	73/473 (15)	40/143 (28)	49/330 (15)	89/473 (19)
Events=104 (%) with NFI	13/28 (41)	8/76 (11)	21/104 (21)	17/28 (61)	35/76 (46)	52/104 (50)

Clinical and Pathological Characteristics of "Patients with event/s": Of the 104 patients detected with events 71(68%) belonged to MB group and received WHO-MB-MDT. Applying Ridley-Jopling Classification, they were mainly BT=53 (53/71=73%), BB=12 (17%) and 6 (8.5%) were BL cases; findings supported by histo-pathology in 35 and Slit skin smear 57 cases. In this study maximum interval between RFT and EX-3 was 9 years. It was noted that frequency of deleterious events did not significantly vary among those who were followed up to 3 years, up to 3-5 years, up to 5-7 years and up to 7-9 years, which indirectly imply that such events continue to occur. (Table 11).

Family history of Leprosy: In the "examined" as well as "Patients with events", presence of a leprosy - affected family member was significantly higher in SA2 (22%) than SA1 (14%) (p=0.5).

Level of Nerve Function Impairments (NFI/ Deformity Grades 1 and 2): NFI in the "eligible", "examined" and in "Patients with events" in SA1and SA2 is given in Table 12. NFI recorded at registration (at HP/PHC) and at examination by the study team was compared for the "examined", and those with and without "events":

a) In the "examined" group at EX-1, 141/577 (24%) were seen with NFI by Study Team. Proportion of patients seen with Grade 2 deformity (visible deformity) was much higher (122/141=87%) than Grade 1, i.e., only sensory impairment (in 19/141=13%).

b) Frequency of NFI was 2-3 times higher in SA1 area subjects than SA2 area subjects in the "examined" as well as those detected with "events".

c) In SA1 area subjects, NFI frequency recorded by HPs and by the team was similar; 36% and 33% respectively. In SA2, the corresponding figures were 8% and 21% respectively and lastly.

d) Among "Patients with events" in SA1 and SA2, NFI was 46% and 11% at baseline while at the point of examination it was 61% and 46% respectively.

Laboratory investigations: During this study, Slit-skin smears were done in 58 cases seen with events. Bacteriology was positive in 11; BI of 1+ to

4+ were recorded in seven, and BI >4+ was recorded in four cases. None of the patient in the "examined" group showed an increase in BI during the three-year study period.

Discussion

Post-RFT deleterious events such as relapse, lepra reaction, neuritis and silently progressing neuropathy are known. However, the extent of the problem/s, individually and collectively has not been studied under the Indian public health set-up, where WHO-recommended regimens are followed, but without emphasis on surveillance. In this study estimation of post RFT deleterious events under the public health set up in select urban and rural areas of Maharashtra was undertaken to gage the extent of problem.

Extent of problem

During three home visits by the team a total of 104 patients including 5 children below age 14, were detected with deleterious events in the 577RFT cases examined. The frequency of events was similar in the urban and rural areas and between PB and MB treatment groups. Notably the proportion of females detected with events was higher than males, could be a fall out of active search method followed. One drawback of the study is; a large chunk (68%) of RFT patients in the urban area (SA1) were lost to follow-up. However, it should be noted that the sampling conditions were found to satisfactory in both SA-1 and SA-2 in the context of severity/ extent of disease when classified into MB and PB groups.

This study has brought out some points worthy of consideration by the public health authorities and proponents of MDT for eliminating leprosy as a public health problem. Most patients with events (>70%) belonged to the economically productive age group (between 15 and 50 years). The event duration was more than one year in 11%. A higher proportion of patients with events (68%) belonged to MB treatment group but had BT and BB type of leprosy (BT=73% and BB=17%).

Neuritis was the most common event seen (N=64), followed by relapse (N=54) and reaction (N=26); such events require prompt medical attention and are usually amenable to therapy. Multiple events were not uncommon, occurring in almost 60%. Further, 26% **(**27/104) patients reported repeat deleterious events mostly neuritis and/orreaction for which they had sought treatment most commonly at an NGO, or privately; a very small minority at HP/PHCs. It is observed that patients with a past history of reaction or neuritis are at a higher risk of developing a repeat episode and form a high risk group. Relapse, on the other hand, was detected for the first time, through this study in all, except two patients. From the patients point of view, the chief anxiety was persistence of hypopigmented (though inactive) lesions on the exposed parts of the body (*viz*. face and arms). This was seen in ~ 5% of patients with events, particularly those with borderline leprosy.

Relapse

This is also the first study of its kind to actively search for three consecutive years, for relapse in a cohort of MB and PB group of patients released from treatment between 2005 and 2010 in public health facilities. Out of 520 RFT patients who had taken full course of treatment 54 (10.4%) were detected with relapse. Incidence of relapse was non-significantly higher in MB group (MB=11.7% PB=8.3% p=0.2), point to be noted here is that (62%) had BT-BB leprosy and had received 12 months of MB-MDT. This implies that both the groups have nearly similar risk of relapse when treated with current six and 12 month duration regimens. Such conclusion can only be drawn if duration of follow-up is also similar and numbers are adequate for comparison.

It is arguable whether clinical signs such as reappearance of lesions and increase in size of old lesions, and appearance of new lesions are reliable indicators of relapse rather than late-onset T1R (Pannikar et al 1989). In this study histopathology could not be undertaken in all since many refused. On the other hand histo-pathology also has its own limitations. It certainly aids in diagnosis but a relapse cannot be ruled out on the basis of a negative report. Secondly, relapse presenting with T1R is not uncommon. Patients presenting with signs of reaction were treated with 3 months regimen of cortico steroids first. Relapse presenting as T1R was found in 23 BT-BB cases. The possibility of relapse in patients with only neuritis and/or silently progressing neuropathy as an 'event' also remains unadd-ressed. Our earlier studies have shown the presence of live *M. leprae* in post-MDT treated tuberculoid cases (Shetty et al 2001). A recent study from our centre shows that viable bacteria are an essential component of T1R (Save et al 2016). Thus it would be all the more difficult to distinguish between relapse and T1R in the borderline spectrum of disease. Such distinction may not be therapeutically relevant if viable bacteria are detectable in both the groups, and MDT would be required.

Parallel study done at NIE centre detected relatively smaller number of relapse cases (no= 58) in a larger cohort of 2177 RFT patients across 4 districts in 2 states in South India. The relapse rate was 6.1 per 1000 person-year, was higher among MB as compared to PB i.e. 7.5 *vs* 5.1 per 1000 person-year. In that study, a local team was engaged in the examination process that was carried out only once (Prabhu et al 2015).

WHO estimated that risk of relapse for PB leprosy is higher than that for MB leprosy, *viz*., 1.07% for PB, and 0.77% for MB and 9 years after stopping MDT. Various other studies using person-years of observation estimate the relapse rates ranging from 0.65 to 3.0% for PB and 0.02 to 0.8% for MB leprosy respectively (The Leprosy Unit, WHO 1995). A retrospective study of patients reporting with relapse among those completing WHO-MDT during 1987-2003 was done at Central Leprosy Training and Research Institute, Tamil Nadu. There lapse rates for MB and PB were 0.8% and 1.9% respectively, whereas rates per person-years of follow up were 0.86 and 1.92/1000. The majority of relapses occurred within 3 years after RFT. (Ali et al 2005, Sowmya and Thappa 2009).

Most of the published work (Boerrigter et al 1991, Pattyn et al 1988) and our own studies (Shetty et al 2005, 2011) on referred relapse cases noted that, among BL-LL cases the bacteriological relapse becomes evident 10 to 15 years after RFT. The incubation period for relapse has an inverse relationship with cell-mediated immunity, is shorter among BT than BL cases. In the current study, the occurrence of relapse was marginally higher between 3-5 years post-RFT, which is in agreement with the preponderance of BT cases in the “examined” group.

Change in clinical classification among “Patients with events”

Comparison between PHC record and the finding during interview resulted in change in classifi-cation in 23% (24/104) of subjects. Twelve pre-viously classified as PB cases were reclassified as MB, likewise 12 MB as PB. This could be either due to upgrading or downgrading or due to misclassi-fication at registration.

Nerve function impairments - Grade 1 and Grade 2 deformity

Nerve function impairment (G1+G2 deformity) is the most serious consequence of leprosy. A remarkable finding in this study was that NFI, as per PHC record was 3 times higher in the Urban

(SA1) as compared to Rural (SA2) i.e. 36% and 8% respectively. Additionally, at examination by the team the corresponding figure was 2 times higher for rural (i.e. SA1=33% and SA2=17%). These observations could reflect:

1) under-reporting or failure to detect nerve function impairment in rural set-up.
2) longer delay in diagnosis in the SA1 area populated mostly (>50%) by migrants. The proportion of MB cases was also higher in SA1 as compared to SA2 (Table 2).

Other possible factors such as demography, environment socio-cultural and biological differences between the predominantly (~60%) Adivasi rural population and the out of state migrants residing in the urban study are a did not form part of the study.

Among patients with events, frequency of NFI was higher at baseline (SA1=46% and SA2=11%) and there was further increase noted at the point of detection with events (61% and 46%). This lends support to the findings of Sales et al (2013) that patients presenting with NFI are at a higher risk of developing further deterioration either during or after the RFT. There fore early diagnosis and prompt treatment of reaction episodes remain the chief means of preventing neurological damage.

Other important lessons

Socio-cultural features

Two study areas represented urban and rural settings. As anticipated there were significant differences in the 2 settings with respect to education and economic status. People seeking treatment at the urban set-up were more literate and better employed but with regard to age group there was no difference and >75% of all patients belonged to economically productive age group (>15 to 50 years). Delay in diagnosis probably was more common in the urban area comprising significant proportion of (~50%) migrant populations as compared to rural area where most were Adivasis (~60%).

Quality of data entry in patients cards at PHCs

There were many instances of 'missing data' (~50%) in the PHC records with regard to Reaction and NFI/s. This made it difficult to gauge the true number of patients who developed new events/problems in post-RFT period.

Additionally, treatment drop-out occurring in 56/406 (14%) in the rural set-up (SA2), was not reflected in the PHC records, resulting in over-estimation of treatment compliance. Treatment drop-out was more frequent among single lesion PB cases (7/55=13%).

Among the treatment dropouts 14 were detected with events, of which 8 had down graded clinically. As in the case of, one treatment dropout child case with Single lesion at baseline, was detected with multiple lesions, BL leprosy with BI of 4+.

The probability is that closer monitoring during treatment might have resulted in timely remedial action. Moreover reasons for dropping out of treatment proffered by the patients reflect lacunae in patients understanding of the disease as well as the quality of information imparted at the clinic.

Lastly it is known that the risk of developing leprosy is higher among those with house-hold exposure to it (Van Beers et al 1999). In SA2 in particular ~ 22% of patients had a history of family contact; Relapse or post-RFT events however did not show any association with the presence of a family member with the disease. This suggests that the relapse is the result of reactivation rather

than re-infection of the disease.

Conclusions

- Proportion of patients with post-RFT event/s requiring medical attention was 18%. Neuritis was the most common event, followed by relapse, reaction and silently progressing neuropathy. This highlights the importance of a good surveillance system, and need for expertise in detecting and treating post-RFT events.
- There is a need to improve the quality of data entry in the HP/PHC registers and for regular monitoring of patients during treatment.

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References

1. Ali MK, Thort DM, Subramanian M et al (2005). A study on trend of relapse in leprosy and factors influencing relapse. *Indian J Lepr*. **77**: 105-115.
2. Becx-Bleumink M (1992). Relapses among leprosy patients treated with multidrug therapy: Experience in the leprosy control programme of the All Africa Leprosy and Rehabilitation and Training Centre (ALERT) in Ethiopia. Practical difficulties with diagnosing relapses. *Int J Lepr Other Mycobact Dis.* **60**: 421-435.
3. Bell-Krotoski JA and Tomancik E (1987). The repeatability of testing with Semmes - Weinstein monofilaments. *J Hand Surg*. **12**: 155-161.
4. Boerrigter G, Ponnighaus JM, Fine PE et al (1991). Four-year follow up results of a WHO-recommended multiple-drug regimen in paucibacillary leprosy patients in Malawi. *Int J Lepr Other Mycobact Dis.* **59**: 255-261.
5. Brandsma JW (2000). Monitoring motor nerves function in leprosy patients. *Lepr Rev*. **71**: 258-267.
6. Haanpaä M, Lockwood DN, Hietaharju A (2004). Neuropathic pain in leprosy. *Lepr Rev*. **75**: 7-18.
7. National Leprosy Eradication Programme. www.nlep.nic.in.
8. National Leprosy Eradication Programme. Government of India. Central Leprosy Division. Directorate General of Health Services, Nirman Bhavan, New Delhi. Progress Report 2013-14. http://nlep.nic.in/pdf/ Progress%20report%20 31st%20March% 2013-14.pdf accessed on 3 October 2016.
9. Pannikar V, Jesudasan K, Vijayakumaran P et al (1989). Relapse or late reversal reaction. *Int J Lepr Other Mycobact Dis*. **57**: 356-364.
10. Pattyn SR, Groenen G, Bourland J et al (1988). The incubation time of relapses after treatment with multibacillary leprosy with Rifampicin containing regimens. *Eur J Epidemiol*. **4**: 231-234.
11. Prabhu R, Manickam P, Mahalingam VN et al (2015). Relapse and deformity among 2177 leprosy patients released from treatment with MDT between 2005 and 2010 in South India: a retrospective cohort study. *Lepr Rev*. **86**: 345-355.

12. Ridley DS (1955). The bacteriological interpretation of skin smears and biopsies in leprosy. *Trans R Soc Trop Med Hyg*. **49**: 449-452.
13. Ridley DS and Jopling WH (1966). Classification of leprosy according to immunity. Five group system. *Int J Lepr Other Mycobact Dis*. **34**: 255-273.
14. Sales AM, Campos DP, Hacker MA et al (2013). Progression of leprosy disability after discharge: is multidrug therapy enough? *J Trop Med and Int Health*. **18**: 1145-1153.
15. Save MP, Dighe AR, Natrajan M et al (2016). Association of viable *Mycobacterium leprae* with Type 1 reaction in leprosy. *Lepr Rev*. **87**: 78-92.
16. Shetty VP, Wakade AV, Antia NH (2001). A high incidence of viable *Mycobacterium leprae* in post MDT recurrent lesions in tuberculoid leprosy patients. *Lepr Rev*. **72**: 337-344.
17. Shetty VP, Wakade AV, Ghate SD et al (2005). Clinical and histopathological and bacteriological study of 52 referral MB cases relapsing after MDT. *Lepr Rev*. **76**: 241-252.
18. Shetty VP, Thakar UH, D'Souza E et al (2009). Detection of previously undetected Leprosy cases in a defined Rural and Urban area of Maharashtra, Western India. *Lepr Rev*. **80**: 22-33.
19. Shetty VP, Wakade AV, Ghate SD et al (2011). Clinical, bacteriological and histopathological study of 62 referral relapse cases between Jan 2004 and Dec 2009 at Foundation for Medical Research, Mumbai. *Lepr Rev*. **82**: 235-243.
20. Shetty VP, Ghate SD, Wakade AV et al (2013). Clinical bacteriological and histopathological characteristics of newly detected children with leprosy: A population based study in a defined rural and urban area of Maharashtra, Western India. *Indian J Dermatol Venereol Leprol*. **79**: 512-517.
21. Sowmya K and Thappa DM (2009). Relapse in leprosy. *Indian J Dermatol Venereol Leprol*. **75**: 126-135.
22. The Leprosy Unit, WHO (1995). Risk of relapse in leprosy. *Indian J Lepr*. **67**: 13-26.
23. van Beers SM, Hatta M, Klaster PR (1999). Patient contact is the major determinant in incident of leprosy: implications for future control. *Int J Lepr Other Mycobact Dis.* **67**: 119-128.
24. WHO SEA-GLP-2009.4. (2011-2015). Enhanced global strategy for further reducing the disease burden due to leprosy operational guidelines.

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