BMJ open

Risk of disability in pre and post multidrug therapy (MDT) treatment among multibacillary leprosy- Agra MB cohort study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000361
Article Type:	Research
Date Submitted by the Author:	31-Aug-2011
Complete List of Authors:	KUMAR, ANIL; National Institute for Leprosy & Other Mycobacterial Diseases, Biostatistics and Epidemiology GIRDHAR, ANITA; National Institute for Leprosy & Other Mycobacterial Diseases,, Clinical GIRDHAR, bhavneswar; National Institute for Leprosy & Other Mycobacterial Diseases,, Clinical
Primary Subject Heading:	Infectious diseases
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, CHEMOTHERAPY, INFECTIOUS DISEASES, EPIDEMIOLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Dermatopathology < PATHOLOGY

Risk of disability in pre and post multidrug therapy (MDT) treatment among multibacillary leprosy- Agra MB cohort study

Anil Kumar, Anita Girdhar, BK Girdhar

Epidemiology and Clinical Divisions, National JALMA Institute for Leprosy & Other Mycobacterial Diseases (ICMR), Taj Ganj, Agra (U.P.), India-282001

dranil250158@gmail.com

Abstract

Background: Leprosy was known as public health problem due to the disabilities it caused. Although so important but very little was known on risk of disabilities mainly by cross sectional studies reporting disability prevalence. Present study reports risk of disability among multibacillary leprosy patients pre and post-MDT treatment.

Methods: The leprosy patients detected in field surveys were put on MDT and followed up for treatment completion, relapse, reactions and development of disability. Assessment was done clinically. Data collected in about 9 years of follow up has been analyzed. Risk and survival analysis was performed and test of significance used.

Results: The disability was found in 10.4% of the MB cases at detection. The risk of disability among patients with >3 nerves was 3.73 times (95%CI: 1.24-11.2) than in patients with ≤ 2 nerves and delay in treatment of $\geq$36 months caused risk of 2.27 times (95%CI: 1.04-4.96) than among those who sought treatment earlier than 36 months. Incidence of disability post-MDT was found 25.5/1000 person years of follow up; 8.6 in ROM arm, 27.1 in MDT arm and 29.1 in treatment defaulters with slightly higher disability among early defaulters (32.9) than 23.0 among late defaulters. The study therefore clearly suggests that incidence of disabilities although could increase slightly (6.9%) but substantially (27.9%) among early defaulters than in late defaulters.

Conclusion: The important conclusion of the study is that the initiation of treatment for leprosy is a must for reducing risk of disability and treatment delay could increase the risk of disability substantially. However, risk between defaulters and those completed treatment did not differ significantly. It may be possible that pathways of causing disability in some patients might have been set before the treatment could be started. Although treatment by 12 monthly single dose ROM appears to be equally effective as 12 months MDT as the incidence of disability is concerned but default rate could be significantly reduced by ROM treatment under supervision and could thus help curing more leprosy patients and preventing disabilities.

Summary

1. Article Focus

- This article provides unique data on risk of disabilities among MB leprosy patients which severely lacks as of now.
- The research question is therefore to see if MDT significantly prevent occurrence of disabilities. What are key risk factors for disabilities?
- Additionally, does default from treatment significantly increase the risk of disabilities?

2. Key Message

- Disabilities due to leprosy can occur pre and post treatment. In this, it found that 10.1% had visible deformities at pre treatment and 10.4% developed post MDT- treatment.
- Very important outcome of the study is the risk of disabilities in those with completed treatment in comparison to those defaulted from treatment do not differ significantly (27.1 vs. 29.1). However ROM has shown better prevention effect than MDT.
- Study invokes interests in finding out the reasons for this finding, is insufficient treatment, failure of reversal in pathology or fibrosis in nerves leading to disabilities, immune stimulation or depression or drug toxicity. However a bigger ROM group can provide more useful data.

3. Strengths and limitations

- The study of this type needs immense resources and time and data from field based cohorts are lacking particularly on long term follow up.
- Findings are very crucial in modifying our thinking that MDT kills the infection but do not prevent disabilities
- While exploring better treatment regimen, larger groups of ROM could have given more conclusive data.

Introduction

Leprosy continues to be a public health problem due to the disabilities and deformities it causes. It is surprising to note that this being so important, very little is known about the risk of disabilities[1] and even today there is mainly cross sectional studies at population level which reports disability prevalence among leprosy patients. The prevalence of disabilities however varies significantly from place to place.

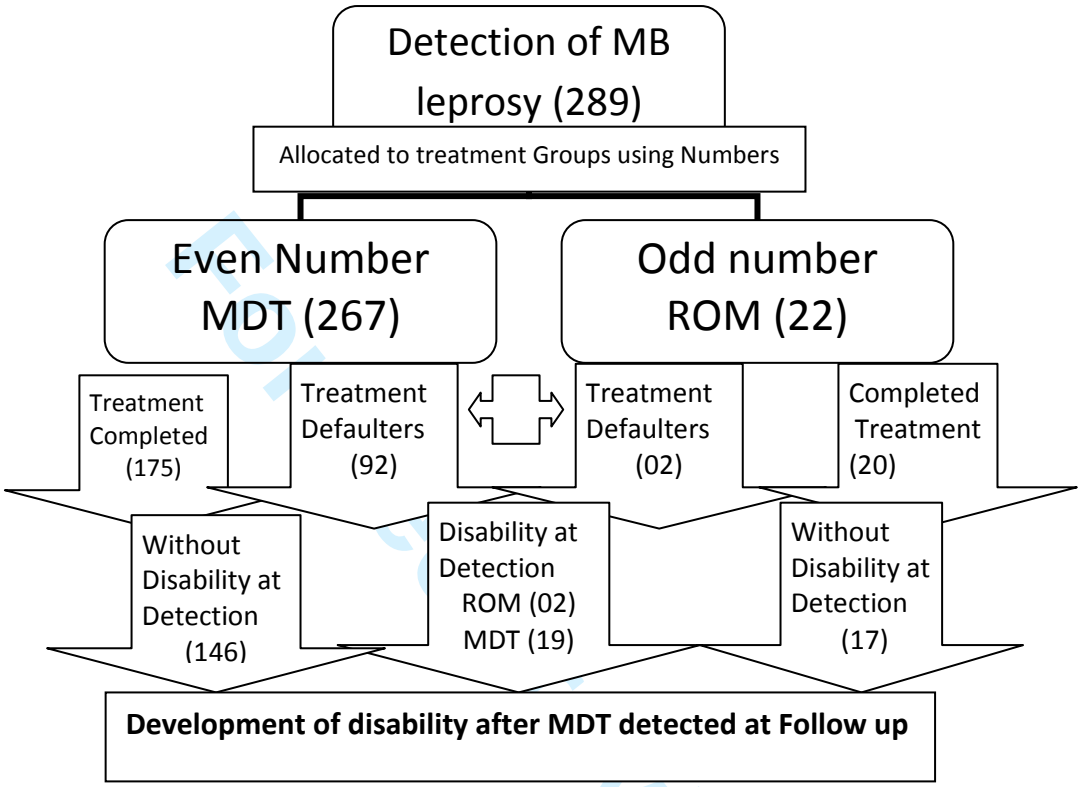
In Malawi, disability prevalence varied from 20% to 10% during 1973 to 1987[1]. A study in South India[2] reported 24.3% visible deformities among patients at registration during 1985 to 1992. The sample surveys undertaken in Agra district during 1999-2006 have reported prevalence of visible deformities from 4.8% to 9.4% in new cases, 17.4% in prevalent cases (History of partial/defaut treatment), 14.9% in rural Agra and 12.7% in urban Agra, 1.8% in new paucibacillary (PB) leprosy and 19.5% in MB leprosy cases[3-5]. A study during 2004-06, detected 1090 leprosy cases in Agra district has shown visible disability of 2.84%; 2.4% among new cases and 19.4% in prevalent cases[6]. However a very few studies on risk of developing disabilities have been undertaken. Although Malawi study[1] had reported risk of developing disabilities as 5/1000 Person years during pre-MDT era and South India study[2] observed disability rate of as 6.8% but this was crude estimate without referring to time. To know the risk of developing disabilities is also very important for the national programme on prevention of disabilities.

This study therefore was attempted to assess the risk/incidence of developing disability among those leprosy patients who had no disability at the time of detection in field surveys but developed it during the years of follow up after completion of W.H.O. multidrug treatment (MDT) and the risk factors for disabilities at (detection) pre and post MDT stage are assessed.

Methodology

During the period of 2001-2006, several active field surveys were undertaken in Agra district in which 293 leprosy cases with multibacillary (MB) leprosy were detected. Of these 293, 4 patients simply did not start the treatment. The study was initially aimed to study the difference in the outcome of the two treatment arms i.e. Rifampicin, Ofloxicin & Minocycline (ROM) and compare with W.H.O. multidrug therapy (MDT) given monthly for 12 months. Since W.H.O. suddenly withdrew ROM supply in 2003, by then only a small number of patients (22) were randomly allocated to ROM arm and later on all the detected cases were put on MDT. Therefore, the study mainly aimed at studying risk of disability among MDT treated cases but attempt is also made to provide a comparative data of ROM vs MDT. An extended version is also attempted to compare the risk of disability among those completed treatment as compared to those defaulted; either early (within 6 months) or late (during 6-11 months). All the cases that were started on treatment were followed up monthly till treatment completion, 6 monthly upto 3 years and then annually till the end of study. Disability Grade 1 was defined as patient developing anesthesia in palm or sole and Grade 2 as visible deformity in either Hand or Feet or eye (Lagophthalmas). During this time, all cases of clinical relapse, reaction and developing of disability

(Grade 1 & Grade 2) were recorded after medical confirmation and necessary medical relief was either provided or referred (see Flow chart). 4 patients from MDT group lost in follow up.



The crude incidence is defined as number of new disabilities at follow up among patients followed up and incidence in 1000 person years of follow up. Follow up of patients continued till March 2011.

The comparison of patients developing disability was done using survival analysis and Log-Rank test to test the significance[7] using SPSS v12 software and Fisher exact test or χ^2 test of significance used to compare proportions[8].

Results

Prevalence of Disability at detection

The prevalence of grade 2 disability (visible) was found to be 10.4%; 13.6 % in patients allocated to ROM arm and 10.1% in MDT arm. The prevalence of Grade 2 disability seems to rise slowly with increased age and male patients had higher disability (14.5 vs. 3.6, $\chi^2 = 8.8$, $p<0.01$) than among the female patients. The Prevalence of disability also increased among patients who delayed treatment for longer period

particularly beyond 36 months (χ^2 = 6.2, p<0.05), significantly high disability noted among patients with 3 or more thickened nerves (χ^2 = 9.5, p<0.01), and among patients with advance clinical stage of disease (BL/LL or Neuritic) (χ^2 = 37.9, p<0.001) than among those with disease of early stage (BT/BB) (Table 1.).

Crude Incidence of disability post MDT (CID)

The patients had been continuously followed during and after the treatment or till they defaulted or lost to follow up. During this time, 1 patient developed disability within 2 years after MDT treatment completion, 8 in 2-4 years, 4 in 4-6 years and 3 after 6 years post MDT completion. Among treatment defaulters at various stages, 1 developed disability within 2 years, 1 in 2-4 years, 3 in 4-6 years and 3 after 6 years from defaulting MDT treatment.

The crude incidence of disability is presented in Table 2. The crude incidence of disability (CID) was observed to be 13.3% among treatment defaulters higher than 10.4% among those completed treatment. This was not significantly different (p>0.05) nor it had increased significantly by age of patients (p>0.05). Although the males had higher incidence of disability than in females (14.3 vs. 12.5 in defaulters and 12.9 vs. 6.3 in completed treatment group) but difference was not significant (p>0.05). The CID was found to be significantly high among MDT patients with neuritic leprosy (Patch 0) or with >10 patches (χ^2 = 15.0, p=0.002) and also in patients with 3 or more thicken nerves and still defaulted (χ^2 = 6.9, p=0.031) but not among those MDT patients who completed their treatment. Patients in MDT arm who had disease of high clinical spectrum like BL/LL/Neuritic leprosy were also observed to have high incidence of disability (χ^2= 20.3, p<0.0001) and but no difference was found by smear positivity status.

Risk factors for prevalence of disability at detection

Using logistic regression analysis, the attempt was made to assess the role of risk factors known to be responsible for causing disability. It was found that patients with 3 or more nerve involvement at the time of detection had 4.53 time risk of disability (OR=4.53, 95%CI: 1.54-13.4) presenting at detection and after adjusting the effect of age and delay in treatment, this showed (OR=3.73, 95%CI: 1.24-11.2). The second higher risk factor was found to be 'delay at detection" for treatment beyond 36 months i.e. (OR=2.27, 95%CI: 1.04-4.96) than among those who started treatment within 36 months of having disease-after adjusted for age (Table 3).

Risk Factors for incidence of disability post MDT

The risk of incidence of disability was assessed among those who were free from disability at the time detection. It was found again that incidence of disability was high (OR=3.05, 95%CI: 1.10-8.48) among patients with 3 or more nerve involvement and remained so (OR=2.81, 95%CI: 1.0-7.9) when standardized for age and delay in treatment (Table 4).

Incidence of disability post MDT

A detailed analysis on incidence of disability has been presented using survival analysis among different groups. The overall incidence of disability was found to be 16.2/1000 person years with mean follow up of 6.99 years after treatment completion or default (Table 5).

Comparison between ROM and MDT arms: The incidence of disability was found to be higher among patients who were in the MDT arm of treatment (27.1/1000 person years) than among those in ROM arm (8.6/1000 person years). The comparison of incidence curve (Figure 1) by years of follow up did not suggest significant difference between the two treatment groups, (Log Rank test =3.19, p=0.074).

Comparison between treatment defaulters with those completed treatment

The incidence of disability among defaulters was higher (29.1/1000 persons years) than among those who completed their treatment (27.1/1000 person years) but there was no statistically significant difference (Log Rank test=.02, p=0.88), See Figure 2. A further analysis between early defaulters and late defaulters, although showed that early defaulters had higher incidence of disability (31.9/1000 person years) than those defaulted late. Further analysis on incidence curve over the years of follow up did not statistically differentiate (p>0.05) the two group (See Figure 3 and 4).

Discussion

This long term study under field conditions had provided unique opportunity to assess the role of factors associated with prevalence of disability at case detection stage in active surveys and also the incidence of disability when patients with varying treatment status are followed up for years. The risk factors for the development of disability among MB patients appeared to be almost similar with increase nerve thickening (≥3 nerves) as number one risk factor and delay in treatment beyond 36 months as number 2 risk factor. A study conducted to assess the risk of paralytic deformity (Grade 2 & above) among cases detected in surveys has also shown that patients with skin lesions and 3 -5 nerves had very high risk

(OR=33.4) of deformity[9]. However, the patient with neuritic leprosy (No skin lesion) with delay in diagnosis for treatment of beyond 5 years had 17.5 times (OR) risk of developing deformity than among those with lesser delay[9].

The incidence of disability among these patients was found to be 25.5/1000 person years of follow up; 8.6 in ROM arm, 27.1 in MDT arm and 29.1 in treatment defaulter with slightly higher disability among early defaulters (31.9) and 23.0 among late defaulters. The study therefore clearly suggests that incidence of disability could increase only slightly (29.1 vs. 27.1) if treatment of the disease is not completed. However, the risk of developing disability in this study was found higher than in Malawi study (5/1000 person years) [1]. The crude incidence of disability in this study was also high (10.4%) among those taken complete MDT treatment than 6.8% in South India Study[2] conducted during 1985-1992. It seems that pathways to cause disability in atleast some of the patients were already set in but not visible at the time of detection, that is why some patients developed disability even after treatment with MDT. The electrophysiological studies of nerves in normal leprosy patients without palpable nerves by routine examinations had revealed that 16% of ulnar nerves and 20% of median nerves electrically abnormal[10]. This helps explain the reasons for higher incidence of disability in patients. In addition, in cases of progressive disease related disabilities – pathology may not get reversed due to ineffectiveness of therapy, may be due to insufficiency of treatment in some cases, nerve fibrosis , immune stimulations and drug toxicity. Some factors like poor physical health, poverty and work conditions could also be contributing to some extent.

Conclusion

The important conclusion of the study is that the early initiation of treatment for leprosy is a must for reducing risk of incidence of disability and delay would increase the risk of disability by many folds. Important is to note that risk of disability between defaulters and those completed treatment is not found significantly different. The complete treatment by 12 monthly single dose ROM treatment may appears to be more effective than of the 12 full months MDT treatment as the incidence of disability is concerned. The ROM also reduced the default rate significantly if patients were given single dose ROM for treatment under supervision and could thus help curing more leprosy patients. A study on single lesion paucibacillary leprosy had also revealed that ROM was highly effective in curing patients of single lesion leprosy (92% at 2 years)[11]. Additionally ROM treatment could help to reduce cost of treatment in comparison of MDT and therefore time is ripe to rethink about introducing ROM in leprosy control programme where disease is still endemic. ROM is certainly operationally convenient, has better

acceptance and thus can help largely in curing bulk of leprosy patients at early stage of disease and help preventing disabilities. The study also provide lead to think if damage for disability was already set in before the treatment started and treatment could only prevented the infection. This is supported by the fact that 16-20% nerve could be abnormal when electrophysiology is done in leprosy patients with normal nerves[10].

Contributors: Dr Anil Kumar was responsible for planning, conducting field study, analysis, writing; Dr Anita Girdhar for clinical evaluation and Dr. BK Girdhar for overall supervision, clinical monitoring and report preparation.

Conflict of interests: None

Funding: Intramural institutional funding.

Acknowledgement: Authors gratefully acknowledges the help extended by the institute by providing internal grant for the study. Thanks are also due to all patients who cooperated in the study and the paramedical workers and District leprosy officer for the support.

References

1. Ponnighaus IM, Boerrigter G, Fine PEM, et al. Disabilities in leprosy patients ascertained in a total population survey in Karonga District, Northern Malawi. Lepr Rev 1990; 61:366-74.
2. Selvaraj G, Prabhakar N, Muliyil J, et al. Incidence of disabilities among multibacillary cases after initiation of multidrug therapy and factors associated with the risk of developing disabilities. Ind J Lepr 1998(suppl); 70:11S-16S.
3. Kumar A, Yadav VS, Girdhar A, et al. Some Epidemiological Observations on Leprosy in Agra, India. Int J Lepr **2001,69(3):234-240.**
4. Kumar A, Girdhar A, Girdhar BK. Epidemiology of Leprosy in Urban Agra, India. Lepr Rev 2003; 74:31-34.
5. Kumar A, Girdhar A, Girdhar BK. Prevalence of leprosy in Agra district (U.P.) India during 2001-2003. Int J Lepr 2005, 73(2):115-121.
6. Kumar A, Girdhar A, Chakma JC, et al A rapid survey for Leprosy in Agra District (2004-06): Epidemiological Observations. J Commun Diseases; 2008
7. Statistical Package for Social Sciences (SPSS) , version 12, 2006.
8. Le Chap T. Applied Catagorical data analysis, John wiley & Sons (USA) 1998.
9. Kumar A, Girdhar A, Girdhar BK. Nerve thickening in leprosy patients and risk of paralytic deformities: a field based study in Agra , India. Leprosy Review (2004) 75,135-42.
10. Husain S, Malaviya GN. Ealy nerve damage in leprosy: An electrophysiological study of ulnar and median nerves in patients with and without clinical neural deficit. Neurology India, 2007;55(1):22-26.
11. Girdhar A, Kumar Anil, Girdhar B.K. A randomised controlled trial assessing the effect of adding clarithromycin to Rifampicin, ofloxacin and minocycline in the treatment of single lesion paucibacillary leprosy in Agra District, India. Lepr Rev 2011, 82:1-10.

Table 1: Prevalence of Grade 2 disability at detection in multibacillary (MB) leprosy patients by Demographic and Clinical status, Agra district (UP) India during 2001-06

Charaecterstics	MDT Arm (267)		ROM arm (22)		Total	
	Cases	Percent Grade 2 Disability	Cases	Percent Grade 2 Disability	Cases	Percent Grade 2 Disability
Age ≤14	17	5.9	01	0	18	5.6
15-24	25	4.0	03	0	28	3.6
25-34	40	5.0	04	0	44	4.6
35-54	108	13.9	07	14.3	115	13.9
>54	77	10.4	07	28.6	84	10.7
Total	267	10.1	22	13.6	289	10.4
Mean (SEM)	43.4(1.1)		42.9(3.8)		43.3(1.0)	
Median	45.0		45.0		45.0	
Sex Male	163	14.1	16	18.8	179	14.5
Female	104	3.9	06	0	110	3.6
Delay in detection (months) ≤12	67	6.0	3	0	70	5.7
13-36	103	8.7	11	0	114	7.9
>36	97	14.4	8	37.5	105	16.2
Patches 0	12	50.0	0	0	12	50.0
1-5	16	25.0	0	0	16	25.0
6-10	84	3.6	8	12.5	92	4.3
>10	155	9.0	14	14.3	169	9.5
Nerves 0-2	99	4.0	10	0	109	3.7
3-5	101	11.9	8	25.0	109	12.8
>5	67	16.4	4	25.0	71	16.9
Clinical status						
BT/BTR	131	3.8	17	11.8	148	4.7
BB/BBR	74	5.4	0	0	74	5.4
BL/LL	51	25.5	5	20.0	56	25.0
N	11	45.5	0	0	11	45.5
Treatment status						
Defaulters	92	8.7	02	50.0	94	9.6
Completed	175	10.9	20	10.0	195	10.8
Smear +ve	27	7.4	02	50.0	29	10.3
-Ve	138	6.5	20	10.0	158	7.0
Not done	102	15.7	00	0	102	15.7

Table 2: Crude incidence of disability (CID) by Demographic and Clinical status at Follow-up among multibacillary (MB) leprosy patients by treatment compliance status , Agra district (UP) India

	Completed Treatment		Defaulters		$\chi 2$ with p-value	
Charaecterstics	Cases	CID rate	Cases	CID rate	Defaulters	Completed Treatment
Age ≤14	12	0	2	0		
15-24	15	6.7	3	33.3		
25-34	31	9.7	9	0	>0.05	>0.05
35-54	66	15.2	25	12.0		
>54	40	7.5	21	19.0		
Total	164	10.4	60	13.3		
Sex Male	101	12.9	28	14.3	>0.05	>0.05
Female	63	6.3	32	12.5		
Delay in Treatment (months)						
≤12	45	6.7	15	6.7	>0.05	>0.05
13-36	62	11.3	26	11.5		
>36	57	12.3	19	21.1		
Patches						
0	5	60.0	0	0		
1-5	6	0	4	0	>0.05	15.0,
6-10	62	6.5	13	0		0.002
>10	91	11.0	43	18.6		
Nerves						
0-2	66	4.5	28	7.1	6.9,	>0.05
3-5	60	11.7	17	5.9	0.031	
>5	38	18.4	15	33.3		
Clinical status						
BT/BTR	96	4.2	24	8.3		
BB/BBR	39	12.8	23	21.7	>0.05	20.3,
BL/LL	24	20.8	13	7.7		<0.0001
N	5	60.0	0	0		
Smear						
+ve	101	8.9	28	17.9	>0.05	>0.05
-Ve	19	10.5	4	0		
Not done	44	13.6	28	10.7		

Table 3: Risk factors for Prevalence of disability using data at detection			
	Odd Ratio (95%CI)	Odd Ratio (95%CI)	Odd Ratio (95%CI)
Nerves 0-2 3 or more	1.0 4.53(1.54-13.4)	1.0 3.87(1.30-11.6)	1.0 3.73(1.24-11.2)
Age <35 ≥35	--	1.0 2.49(0.83-7.50)	1.0 2.35(0.77-7.12)
Delay in treatment (mo) ≤36 >36	--	--	 1.0 2.27(1.04-4.96)
Standardized for	none	Age	Age & delay in treatment

Table 4: Risk factors for Incidence of disability post multidrug therapy			
	Odd Ratio (95%CI)	Odd Ratio (95%CI)	Odd Ratio (95%CI)
Nerves 0-2 3 or more	1.0 3.05(1.10-8.48)	1.0 2.84(1.01-8.0)	1.0 2.81(1.0-7.90)
Age <35 ≥35	--	1.0 1.63(0.57-4.58)	1.0 1.64(0.58-4.68)
Delay in treatment (mo) ≤36 >36	--	--	 1.0 1.22(0.57-2.61)
Standardized for	none	Age	Age & delay in treatment

Table 5: Incidence of disability /1000 Person years of follow up					
Treatment Group	Cases	Mean Years Survival Time	Persons Years (PY)	Disability developed in	Incidence/ 1000 PY
ROM – Completed Treatment	17	6.82	115.9	01	8.6
MDT- Completed Treatment	142	4.16	590.7	16	27.1
Defaulters of MDT	58	4.74	274.9	08	29.1
Early (<6 months of Treatment)	37	5.08	188.0	06	31.9
Late (6-11 month of Treatment)	21	4.14	86.9	02	23.0
All	217	4.52	981.5	25	25.5

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

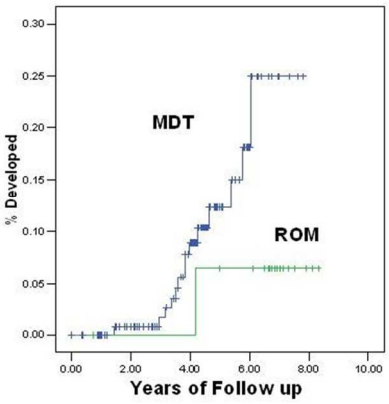
Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	5
		(c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	5-7
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

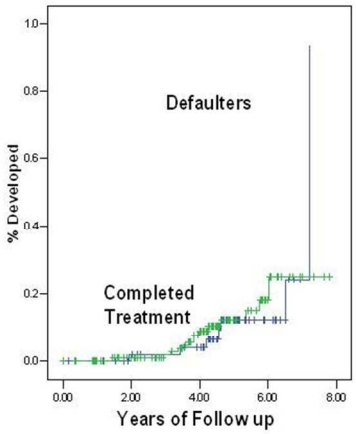
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Figure 1: Risk of developing disability among MB leprosy patients after multidrug therapy



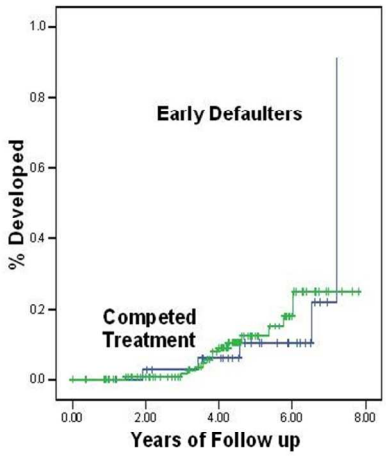
MDT Vs. ROM
254x190mm (96 x 96 DPI)

Figure 2: Risk of developing disability among MB leprosy patients post MDT by Treatment compliance



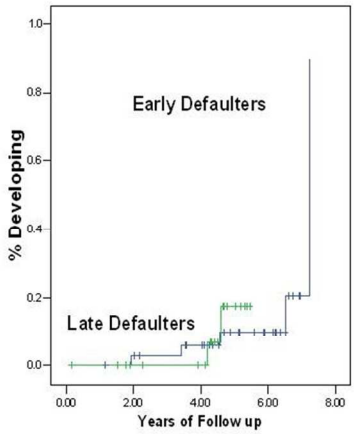
Defaulters vs. completed treatment
254x190mm (96 x 96 DPI)

Figure 3: Risk of developing disability among MB leprosy patients post multidrug therapy



Early defaulters vs. complete treatment
254x190mm (96 x 96 DPI)

Figure 4: Risk of developing disability among MB leprosy patients who defaulted from MDT



Early defaulters vs. late defaulters
254x190mm (96 x 96 DPI)

Risk of disability in pre and post multidrug therapy (MDT) treatment among multibacillary leprosy- Agra MB cohort study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000361.R1
Article Type:	Research
Date Submitted by the Author:	14-Dec-2011
Complete List of Authors:	KUMAR, ANIL; National Institute for Leprosy & Other Mycobacterial Diseases, Biostatistics and Epidemiology GIRDHAR, ANITA; National Institute for Leprosy & Other Mycobacterial Diseases,, Clinical GIRDHAR, bhavneswar; National Institute for Leprosy & Other Mycobacterial Diseases,, Clinical
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Dermatology, Epidemiology, Evidence based practice, Health informatics, Health services research
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, CHEMOTHERAPY, INFECTIOUS DISEASES, EPIDEMIOLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Dermatopathology < PATHOLOGY

Risk of developing disability after multidrug therapy (MDT) treatment among multibacillary leprosy

Anil Kumar, Anita Girdhar, BK Girdhar

Epidemiology and Clinical Divisions, National JALMA Institute for Leprosy & Other Mycobacterial Diseases (ICMR), Taj Ganj, Agra (U.P.), India-282001

dranil250158@gmail.com

Abstract

Objectives: Leprosy is known due to disabilities it causes. Surprisingly very little is known about risk of disabilities. Even today, mainly cross-sectional studies reports disability prevalence. Present study aims to report risk of disability among multibacillary leprosy patients after treatment with WHO-MDT.

Methods: The study design is prospective and setting is institutional field area. Patients detected during 2001-2006 in surveys. 289 multibacillary patients and 162 completed study. Both sexes were involved. Primary outcome planned was to study cure of disease, relapses and disability in two arms of MDT and ROM. Secondary outcome was to measure reaction and default. Assessment was done clinically. Data has been analyzed using SPSS software, Logistic, survival analysis was performed and χ^2 test of significance used.

Results: Important risk factor found is $\geq$3 nerves involved with odds of 3.73(1.24-11.2) and delay in treatment; 2.27(1.04-4.96) at pre-MDt stage and $\geq$3 nerves involved with odds of 2.81(1.0-7.9) at post-MDT stage. Incidence of disability was found to be 2.54/100 person years; 0.92 in ROM arm, 2.69 in MDT arm and 2.84 in defaulters with slightly higher disability among early defaulters (3.08) than 2.30 among late defaulters. The study suggests that incidence of disability could increase slightly, 17% (2.84 vs. 2.42) if treatment is not completed.

Conclusion: Early treatment for leprosy is a must for reducing risk of disability and treatment delay would increase the risk of disability by manyfolds. Important is to note that risk of disability between defaulters and those completed treatment is not found significantly different. Although complete treatment by 12 monthly single dose ROM may appear to be as effective as 12 months MDT for new disability to occur but default rate could be significantly reduced if single dose ROM is given under supervision and could help curing more leprosy patients and helps leprosy control programme.

Introduction

Leprosy is known as public health problem due to the disabilities it causes. It was surprising to note that this being so important, very little was known about the risk of disabilities[1] and even today there is mainly cross sectional studies at population level which reports disability prevalence among leprosy patients. The prevalence of disability however varies significantly from one study to another. In Malawi study, disability prevalence varied from 20% to 10% during 1973 to 1987[1]. A study in South India[2] reported 24.3% visible deformities among cases at registration during 1985 to 1992. The studies undertaken in Agra districts during 1999-2006 have reported prevalence of visible deformities from 4.8% to 9.4% in new cases, 17.4% in prevalent cases (History of partial/defaut treatment), 14.9% in rural Agra and 12.7% in urban Agra, 1.8% in new paucibacillary (PB) leprosy and 19.5% in MB leprosy cases[3-5]. A study during 2004-06, detected 1090 leprosy cases in Agra district has shown visible disability of 2.84%; 2.4% among new cases and 19.4% in prevalent cases[6]. However a very few studies on risk of developing disabilities have been undertaken. Although Malawi study[1] had reported risk of developing disabilities as 5/1000 Person years during pre-MDT era and South India study[2] observed disability rate of as 6.8% but this was crude estimate without referring to time. The risk of developing disabilities is also very important for the national programme on prevention of disabilities.

This study therefore was attempted to assess the risk/incidence of developing disability among those leprosy patients who had no disability at the time of detection in field surveys but developed it during the years of follow up after completion of W.H.O. multidrug treatment (MDT).

Design and Methods

This study was planned as a randomized field trial aimed at comparing cure and relapse in standard 12 monthly fixed multidrug therapy (MDT) with that of 12 monthly single dose of rifampicin**,** ofloxacin and minocycline (ROM) among MB leprosy patients detected in the field. Since ROM was suddenly discontinued by W.H.O. from the programme and only 22 cases were randomly allocated to ROM arm by then, there after only MDT was given to all detected cases and prospectively followed up.

Study site, field setting and duration of study

The study was started in our field are in Agra District of Uttar Pradesh on patients detected in field survey under several studies on prevalence of leprosy during 2001-2006[3-6]. The Agra District is located 200 KM away from Delhi and spread in the radius of 100 KM on either side in length and borders with district Itawa & Firozabad on eastern side, Mathura & Bharatpur on north-west side and Gwalior & Dholpur on south side. Several studies were undertaken since the district was highly endemic for leprosy with prevalence of 16.4/10000 during 2001-03 and 7/10000 during 2004-06. The present study was based on patients detected in such surveys conducted during 2001-06 and all patients were followed up till April 2011.

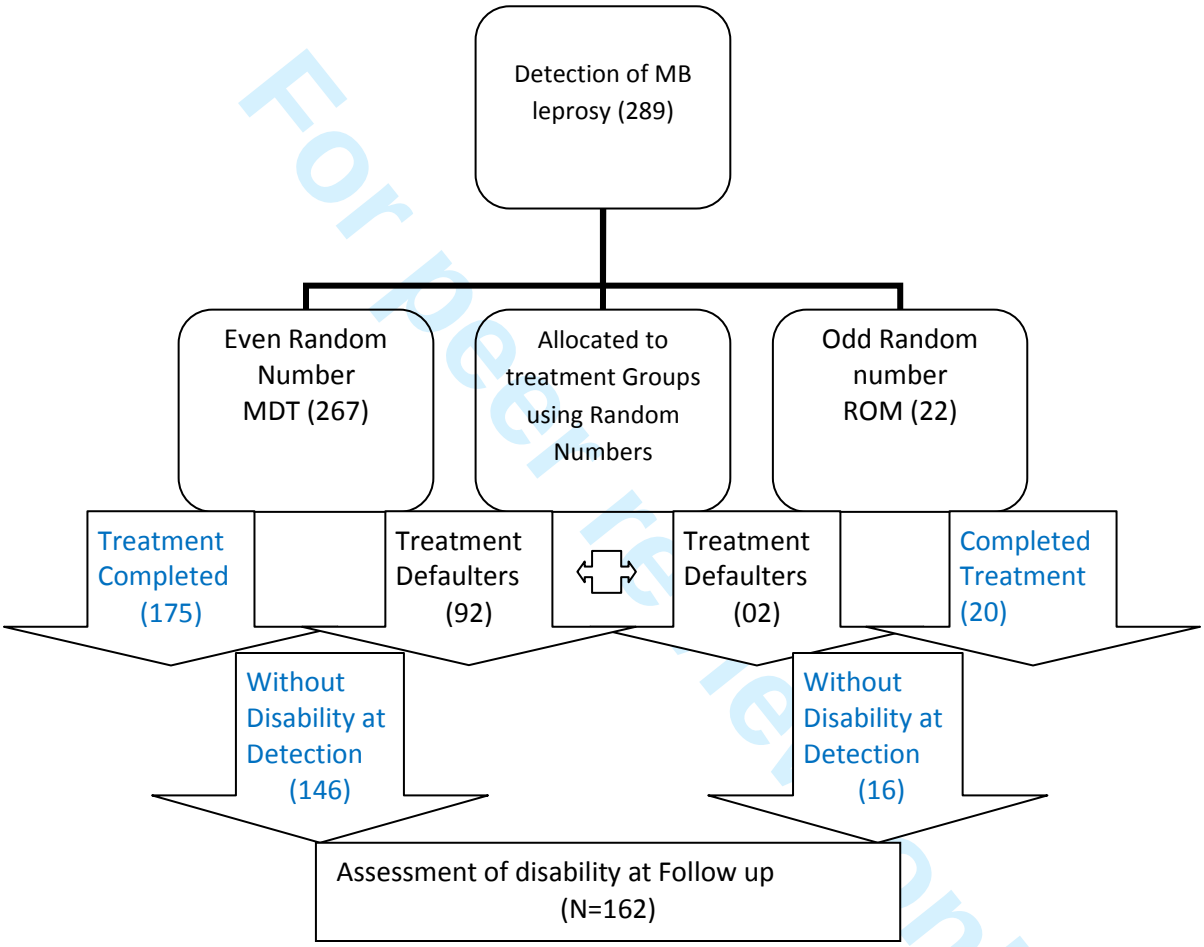
Inclusion/Exclusion criterion of Patients for the study

Newly detected leprosy patients diagnosed clinically as multibacillary (MB) leprosy were taken for the study. This included patients with >5 skin lesions, either erythmatous or hypo-pigmented with definite impairment or loss of sensations (tested with ball point pen) or >2 thickened nerves. None of the patients had taken leprosy treatment earlier. Children below 5 and adults above 70 were although treated as per norms but not included in the study and so were the pregnant and lactating women.

Cohort size and treatment allocation and Assessment on Follow up

A total of 293 leprosy cases with multibacillary (MB) leprosy were detected. Of these 293, 4 patients did not start the treatment. The study was initially aimed to study the difference in the outcome of the two treatment arms (100 patients in each arm) i.e. Rifampicin 600mg, Ofloxacin 400 mg & Minocycline 200 mg (ROM) for adult and half of it for children (<15 years) as recommended by WHO vs. W.H.O. standard multidrug therapy (MDT: Rifampicin, Ofloxacin and Dapsone) given monthly for 12 months but since W.H.O. suddenly withdrew ROM supply in 2003, by then only a small number of patients (22) were randomly (Using random number table) allocated to ROM arm and later on all the detected cases were put on MDT. Therefore, the study mainly aimed at studying risk of relapse and disability among MDT treated cases but attempt is also made to provide a comparative data of ROM vs MDT. An extended version is also attempted to compare the risk of disability among those completed treatment as compared to those defaulted; either early (within 6 months) or late (during 6-11 months). All the cases that were started on treatment were followed up monthly till treatment completion, 6 monthly upto 3

years and then annually till the end of study. Disability Grade 1 was defined as patient developing anesthesia in palm or sole tested with a ball point pen and Grade 2 as visible deformity in either Hand or Feet or eye (Lagophthalmas). During this time, all cases of clinical relapse, reaction and developing of disability (Grade 1 & Grade 2) were recorded after medical confirmation and necessary medical relief was either provided or referred (see Flow chart).



Ethical Approval and informed consent

Ethical Approval was taken from Institutional ethical committee who was being informed periodically about the progress of the work. All the patients were informed about the possible side effects, remedies and benefits. Although the treatment given was WHO standard regimen but for reasons of follow up etc patients were asked to consent and then they were put on respective treatment. In case of children, consent of their parents was taken.

Statistical methods

The comparison of patients developing disability was done using survival analysis and Log-Rank test to test the significance[7] using SPSS v12 software and Fisher exact test or χ^2 test of significance used to compare proportions[8]. The logistic regression analysis was done to undertake risk factor analysis.

Results

Demographic Characteristics of patients

The patients of all ages were detected in surveys. The mean age was 43.3 years (SEM=1.0) and median of 45 years. The groups were closely similar. Most patients (68.8%) were aged 35 & above and only 6.2% were the child cases of MB leprosy. Male patients accounted for 61.9% of the total 289 cases in this study. At the time of survey, 24.2% patients were those who reported to acquire leprosy during last 12 months, 39.4% in last 12-36 months and rest had disease since over 36 months.

Prevalence of Disability at detection

The prevalence of grade 2 disability (visible) was found to be 10.4%; 13.6 % in patients allocated to ROM arm and 10.1% in MDT arm. The prevalence of Grade 2 disability seems to rise slowly with increased age and male patients had higher disability (14.5 vs. 3.6, $\chi^2 = 8.8$, $p<0.01$) than among the female patients. The Prevalence of disability also increased among patients who delayed treatment for longer period particularly beyond 36 months ($\chi^2 = 6.2$, $p<0.05$), significantly high disability noted among patients with 3 or more thickened nerves ($\chi^2 = 9.5$, $p<0.01$), and among patients with advance clinical stage of disease (BL/LL or Neuritic) ($\chi^2 = 37.9$, $p<0.001$) than among those with disease of early stage (BT/BB). However the prevalence of disability did not vary significantly among patients who defaulted from treatment than among those who completed treatment ($\chi^2 = 0.45$, $p=0.80$) and by smear status ($\chi^2 = 4.6$, $p=0.10$) . See Table 1.

Crude Incidence of disability (CID)

The crude incidence of disability is presented in Table 2. The crude incidence of disability (CID) was observed to be 13.6% among treatment defaulters higher than 10.5% among those completed treatment but not found significantly different (p>0.05) nor it had increased significantly by age of patients (p>0.05). Although the males had higher incidence of disability than in females (14.3 vs. 12.9 in defaulters and 12.9 vs. 6.6 in completed treatment group) but difference was not significant (p>0.05). The CID was found to be significantly high among MDT patients with neuritic leprosy (Patch 0) or with more than 10 patches (χ^2 = 15.0, p=0.002). The patients with 3 or more thicken nerves and still defaulted had significantly higher disability developed (χ^2 = 7.7, p=0.021) in comparison to those patients on MDT who completed their treatment. Patients in MDT arm who had disease of high clinical spectrum like BL/LL/Neuritic leprosy were observed to have significantly high incidence of disability (χ^2=19.6, p<0.001). However, no difference was found by smear positivity status of patients.

Risk factors for prevalence of disability

Using logistic regression analysis, the attempt was made to assess the role of risk factors known to be responsible for causing disability. It was found that patients with 3 or more nerve involvement at the time of detection had 4.53 time risk of disability (OR=4.53, 95%CI: 1.54-13.4) presenting at detection and after adjusting the effect of age and delay in treatment, this showed (OR=3.73, 95%CI: 1.24-11.2). The second higher risk was found of the factor 'delay at detection" for treatment beyond 36 months i.e. (OR=2.27, 95%CI: 1.04-4.96) than among those who started treatment within 36 months of having disease- adjusted for age (Table 3).

Risk Factors for incidence of disability

The risk of incidence of disability was assessed among those who were free from disability at the time detection. It was found again that incidence of disability was high (OR=3.05, 95%CI: 1.10-8.48) among patients with 3 or more nerve involvement and remained so (OR=2.81, 95%CI: 1.0-7.9) when standardized for age and delay in treatment (Table 4).

Incidence of disability

A detailed analysis on incidence of disability has been presented using survival analysis among different groups. The overall incidence of disability was found to be 2.54/100 person years with mean follow up of 4.46 years after treatment completion or default (Table 5).

Comparison between ROM and MDT arms: **The cure rate in ROM arm was observed to be 93.8%(15/16) in comparison to 81.5%(119/146) in MDT arm. The difference was not significant (p=0.076).** The incidence of disability was found to be higher among patients who were in the MDT arm of treatment (2.69/100 person years) than among those in ROM arm (0.92/100 person years). The comparison of incidence (hazard) curve (Figure 1) by years of follow up did not suggest significant difference between the two treatment groups, (Log Rank test =3.16, p=0.076).

Comparison between treatment defaulters with those completed treatment

The incidence of disability among defaulters was high (2.84/100 persons years) than among those who completed their treatment (2.69/100 person years) but incidence curve did not show statistically significant difference (Log Rank test=.02, p=0.88), See Figure 2. A further analysis between early defaulters and late defaulters, although showed that early defaulters had highest incidence of disability (3.08/100 person years) than 2.3/100 PY in the group of late defaulters but incidence curve over the years of follow up did not statistically differentiate (p>0.05) the two (See Figure 3 and 4).

Discussion

This study provide unique opportunity to assess the role of factors associated with prevalence of disability at case detection stage in active surveys and also the incidence of disability when patients with varying treatment status are followed up for years. The risk factors for the development of disability among MB patients appeared to be almost similar with increase nerve thickening ($\geq$3 nerves) as number one risk factor and delay in treatment beyond 36 months as number 2 risk factor. A study conducted to assess the risk of paralytic deformity (Grade 2 & above) among cases detected in surveys has also shown that patients with skin lesions and 3 -5 nerves had very high risk (OR=33.4) of deformity[9]. However, the patient with neuritic leprosy (No skin lesion) with delay in diagnosis for treatment of beyond 5 years had 17.5 times (OR) risk of developing deformity than among those with lesser delay[9].

The incidence of disability among these patients was found to be 2.54/100 person years of follow up; 0.92 in ROM arm, 2.69 in MDT arm and 2.84 in treatment defaulters with slightly higher disability among early defaulters (3.08) and 2.30 among late defaulters. The study therefore clearly suggests that incidence of disability could only slightly be higher 6% (2.84 vs. 2.69) in the MDT group and 17% (2.84 vs. 2.42) taken ROM & MDT patients together completing treatment than in those defaulting. However, the risk of developing disability in this study was found higher than in Malawi study (5/1000 person years) [1]. The crude incidence of disability in this study was also high (10.4%) among those taken complete MDT treatment than 6.8% in South India Study[2] conducted during 1985-1992. Although the reasons for higher incidence of disability in this study are not clear, but could be attributed, at least partially, to poor physical health, poverty and work conditions.

Conclusion

The important conclusion of the study is that the initiation of treatment for leprosy is a must for reducing risk of incidence of disability and delay in initiating treatment would increase the risk of disability by many folds. Important is to note that risk of disability between defaulters and those completed treatment is not found significantly different. Although complete treatment by 12 monthly single dose ROM treatment may appear to be as effective as 12 full months MDT treatment as the incidence of disability is concerned but default rate could be significantly reduced if patients were given single dose ROM for treatment under supervision and could thus help curing more leprosy patients. A study on single lesion paucibacillary leprosy had also revealed that ROM was highly effective in curing patients of single lesion leprosy (92% at 2 years)[10]. Even in this study, ROM seems to cure more patients than the MDT. Additionally ROM treatment could help to reduce cost of treatment in comparison of MDT and therefore time is ripe to rethink about introducing ROM in leprosy control programme where disease is still endemic as it can help better in preventing disabilities.

Contributors: Dr Anil Kumar was responsible for planning, conducting field study, analysis, writing; Dr Anita Girdhar for clinical evaluation and Dr. BK Girdhar for overall supervision, clinical monitoring and report preparation.

Statement of funding: This study was supported by an institutional grant from National JALMA Institute for Leprosy, Taj Ganj, Agra. No specific funding from external agencies was asked for.

Conflict of interests: None

Acknowledgement: Authors gratefully acknowledges the help extended by the institute by providing internal grant for the study. Thanks are also due to all patients who cooperated in the study and the paramedical workers and District leprosy officer for the support.

References

1. Ponnighaus IM, Boerrigter G, Fine PEM, et. Al.. Disabilities in leprosy patients ascertained in a total population survey in Karonga District, Northern Malawi. Lep Rev 1990; 61:366-374.
2. Selvaraj G, Prabhakar N, Muliyil J, et al. Incidence of disabilities among multibacillary cases after initiation of multidrug therapy and factors associated with the risk of developing disabilities. Ind J Lepr, 1998(suppl); 70:11S-16S.
3. Kumar A, Yadav VS, Girdhar A, et al. Some Epidemiological Observations on Leprosy in Agra, India. Int J Lepr **2001, 69(3):234-240.**
4. Kumar A, Girdhar A, Girdhar BK. Epidemiology of Leprosy in Urban Agra, India. Lepr Rev, 2003; 74:31-34.
5. Kumar A, Girdhar A, Girdhar BK. Prevalence of leprosy in Agra district (U.P.) India during 2001-2003. Int J Lepr ,2005, 73(2):115-121.
6. Kumar A, Girdhar A, Chakma JC, et al. A rapid survey for Leprosy in Agra District (2004-06): Epidemiological Observations. J Commun Dis; 2008,40(4): 277-284
7. Statistical Package for Social Sciences (SPSS) , version 12, 2006.
8. Le Chap T. Applied Catagorical data analysis, John wiley & Sons (USA) 1998.
9. Kumar A, Girdhar A, Girdhar BK. Nerve thickening in leprosy patients and risk of paralytic deformities: a field based study in Agra , India. Lepr Rev, 2004, 75:135-142.
10. Girdhar A, Kumar Anil, Girdhar B.K. A randomised controlled trial assessing the effect of adding clarithromycin to Rifampicin, ofloxacin and minocycline in the treatment of single lesion paucibacillary leprosy in Agra District, India. Lepr Rev, 2011, 82:1-10.

Table 1: Prevalence of Grade 2 disability at detection in multibacillary (MB) leprosy patients by Demographic and Clinical status, Agra district (Uttar Pradesh) India during 2001-06

Charaecterstics	MDT Arm (267)		ROM arm (22)		Total	
	Cases	Percent Grade 2 Disability	Cases	Percent Grade 2 Disability	Cases	Percent Grade 2 Disability
Age ≤14	17	5.9	01	0	18	5.6
15-24	25	4.0	03	0	28	3.6
25-34	40	5.0	04	0	44	4.6
35-54	108	13.9	07	14.3	115	13.9
>54	77	10.4	07	28.6	84	10.7
Total	267	10.1	22	13.6	289	10.4
Mean (SEM)	43.4(1.1)		42.9(3.8)		43.3(1.0)	
Median	45.0		45.0		45.0	
Sex Male	163	14.1	16	18.8	179	14.5
Female	104	3.9	06	0	110	3.6
Delay in detection (months) ≤12	67	6.0	3	0	70	5.7
13-36	103	8.7	11	0	114	7.9
>36	97	14.4	8	37.5	105	16.2
Patches 0	12	50.0	0	0	12	50.0
1-5	16	25.0	0	0	16	25.0
6-10	84	3.6	8	12.5	92	4.3
>10	155	9.0	14	14.3	169	9.5
Nerves 0-2	99	4.0	10	0	109	3.7
3-5	101	11.9	8	25.0	109	12.8
>5	67	16.4	4	25.0	71	16.9
Clinical status						
BT/BTR	131	3.8	17	11.8	148	4.7
BB/BBR	74	5.4	0	0	74	5.4
BL/LL	51	25.5	5	20.0	56	25.0
N	11	45.5	0	0	11	45.5
Treatment status						
Defaulters	92	8.7	02	50.0	94	9.6
Completed	175	10.9	20	10.0	195	10.8
Smear +ve	27	7.4	02	50.0	29	10.3
-Ve	138	6.5	20	10.0	158	7.0
Not done	102	15.7	00	0	102	15.7

Table 2: Crude incidence of disability (CID) by Demographic and Clinical status at Follow-up among multibacillary (MB) leprosy patients by treatment compliance status , Agra district (UP) India

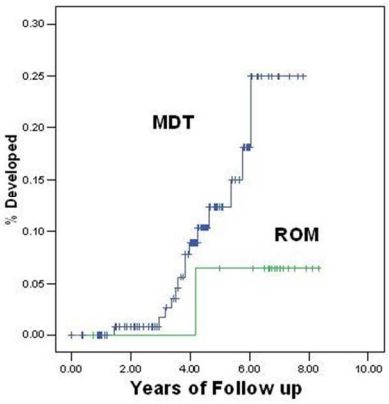
	Completed Treatment		Defaulters		χ2 with p-value	
Charaecterstics	Cases	CID rate	Cases	CID rate	Completed Treatment	Defaulters
Age ≤14	12	0	2	0		
15-24	15	6.7	3	33.3		
25-34	30	9.7	9	0	>0.05	>0.05
35-54	64	15.6	25	12.0		
>54	41	7.3	20	20.0		
Total	162	10.5	59	13.6		
Sex Male	101	12.9	28	14.3	>0.05	>0.05
Female	61	6.6	31	12.9		
Delay in Treatment (months)						
≤12	44	6.8	14	7.1	>0.05	>0.05
13-36	63	11.1	26	11.5		
>36	55	12.7	19	21.1		
Patches						
0	5	60.0	0	0		
1-5	6	0	4	0	15.0,	>0.05
6-10	62	6.5	13	0	0.002	
>10	90	11.1	42	19.0		
Nerves						
0-2	66	4.8	28	7.1	>0.05	7.7,
3-5	60	11.7	17	5.9		0.021
>5	39	17.9	14	35.7		
Clinical status						
BT/BTR	94	4.3	24	8.3		
BB/BBR	38	13.2	23	21.7	19.6,	>0.05
BL/LL	25	20.0	12	8.3	<0.001	
N	5	60.0	0	0		
Smear						
-ve	101	8.9	28	17.9	>0.05	>0.05
+Ve	19	10.5	4	0		
Not done	42	14.3	27	11.1		

Table 3: Risk factors for Prevalence of disability at detection (Pre-MDT stage)			
	Odd Ratio (95%CI)	Odd Ratio (95%CI)	Odd Ratio (95%CI)
Nerves 0-2 3 or more	1.0 4.53(1.54-13.4)	1.0 3.87(1.30-11.6)	1.0 3.73(1.24-11.2)
Age <35 ≥35	--	1.0 2.49(0.83-7.50)	1.0 2.35(0.77-7.12)
Delay in treatment (mo) ≤36 >36	--	--	 1.0 2.27(1.04-4.96)
Standardized for	none	Age	Age & delay in treatment

Table 4: Risk factors for Incidence of disability post multidrug therapy			
	Odd Ratio (95%CI)	Odd Ratio (95%CI)	Odd Ratio (95%CI)
Nerves 0-2 3 or more	1.0 3.05(1.10-8.48)	1.0 2.84(1.01-8.0)	1.0 2.81(1.0-7.90)
Age <35 ≥35	--	1.0 1.63(0.57-4.58)	1.0 1.64(0.58-4.68)
Delay in treatment (mo) ≤36 >36	--	--	 1.0 1.22(0.57-2.61)
Standardized for	none	Age	Age & delay in treatment

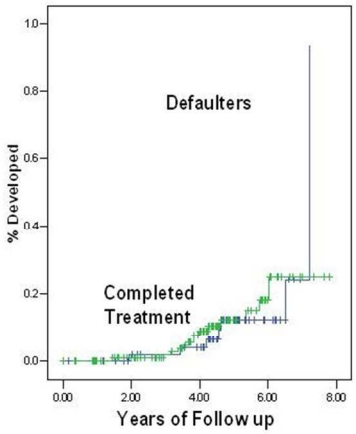
Table 5: Incidence of disability /1000 Person years of follow up					
Treatment Group	Cases	Mean Years Survival Time	Persons Years (PY)	Disability developed in	Incidence/ 100 PY
Completed Treatment ROM MDT	162 16 146	4.37 6.82 4.08	703.7 109.0 594.7	17 01 16	2.42 0.92 2.69
Defaulters of MDT Early (<6 months of Treatment) Late (6-11 month of Treatment)	59 38 21	4.78 5.12 4.14	281.9 194.9 87.0	08 06 02	2.84 3.08 2.30
All	221	4.46	985.6	25	2.54

Figure 1: Risk of developing disability among MB leprosy patients after multidrug therapy



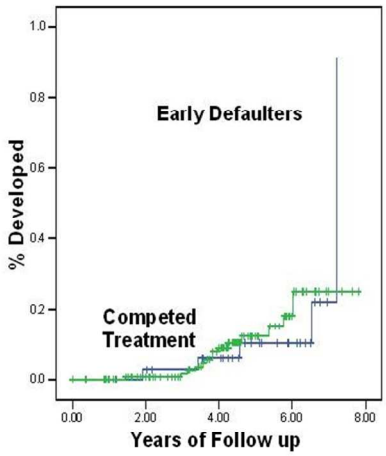
MDT Vs. ROM
254x190mm (96 x 96 DPI)

Figure 2: Risk of developing disability among MB leprosy patients post MDT by Treatment compliance



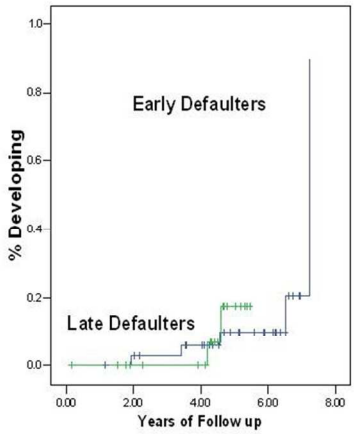
Defaulters vs. completed treatment
254x190mm (96 x 96 DPI)

Figure 3: Risk of developing disability among MB leprosy patients post multidrug therapy



Early defaulters vs. complete treatment
254x190mm (96 x 96 DPI)

Figure 4: Risk of developing disability among MB leprosy patients who defaulted from MDT



Early defaulters vs. late defaulters
254x190mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	5
		(c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	5-7
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Risk of disability in pre and post multidrug therapy (MDT) treatment among multibacillary leprosy- Agra MB cohort study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000361.R2
Article Type:	Research
Date Submitted by the Author:	20-Jan-2012
Complete List of Authors:	KUMAR, ANIL; National Institute for Leprosy & Other Mycobacterial Diseases, Biostatistics and Epidemiology GIRDHAR, ANITA; National Institute for Leprosy & Other Mycobacterial Diseases,, Clinical GIRDHAR, bhavneswar; National Institute for Leprosy & Other Mycobacterial Diseases,, Clinical
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Dermatology, Epidemiology, Evidence based practice, Health informatics, Health services research
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, CHEMOTHERAPY, INFECTIOUS DISEASES, EPIDEMIOLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Dermatopathology < PATHOLOGY

Risk of developing disability in pre and post multidrug therapy (MDT) treatment among multibacillary leprosy –Agra MB cohort study

Anil Kumar, Anita Girdhar, BK Girdhar

Epidemiology and Clinical Divisions, National JALMA Institute for Leprosy & Other Mycobacterial Diseases (ICMR), Taj Ganj, Agra (U.P.), India-282001

dranil250158@gmail.com

Abstract

Objectives: Leprosy is known due to disabilities it causes. Surprisingly very little is known about risk of disabilities. Even today, mainly cross-sectional studies reports disability prevalence. Present study aims to report risk of disability in pre and post WHO-MDT in multibacillary leprosy patients and to assess extent of incidence of disability.

Methods: The study design is prospective and setting is institutional field area. Patients detected during 2001-2006 in surveys. 289 multibacillary patients and 146 completed study. Both sexes were involved. Primary outcome planned was to study cure of disease, relapses and disability in patients received MDT. Secondary outcome was to measure reaction and default. Assessment was done clinically. Data has been analyzed using SPSS software, Logistic, survival analysis was performed and χ^2 test of significance used.

Results: Important risk factor found is $\geq$3 nerves involved with odds of 3.73(1.24-11.2) and delay in treatment; 2.27(1.04-4.96) at pre-MDT stage and $\geq$3 nerves involved with odds of 2.81(1.0-7.9) at post-MDT stage. Incidence of disability was found to be 2.74/100 person years; 2.69 in MDT arm and 2.84 in defaulters with slightly higher disability among early defaulters (3.08) than 2.30 among late defaulters. The study suggests that incidence of disability could be slightly higher if treatment is not completed.

Conclusion: Early treatment for leprosy is a must for reducing risk of disability and treatment delay would increase the risk of disability. Important is to note that incidence of disability between defaulters and those completed treatment is not found significantly different.

Introduction

Leprosy is known as public health problem due to the disabilities it causes. It was surprising to note that this being so important, very little was known about the risk of disabilities[1] and even today there is mainly cross sectional studies at population level which reports disability prevalence among leprosy patients. The prevalence of disability however varies significantly from one study to another. In Malawi study, disability prevalence varied from 20% to 10% during 1973 to 1987[1]. The studies done in India[2-6] reported visible deformities rate from 2.8% to 24.3% among cases at registration or detection in population surveys. However a very few studies on risk of developing disabilities have been undertaken. Although Malawi study[1] had reported risk of developing disabilities as 5/1000 Person years during pre-MDT era and South India study[2] observed disability rate of 6.8% but this was crude estimate without referring to time. The risk of developing disabilities is also very important for the national programme on prevention of disabilities.

This study was therefore attempted to assess the risk/incidence of developing disability among those leprosy patients who had no disability at the time of detection in field surveys but developed it during the years of follow up after completion of W.H.O. multidrug treatment (MDT).

Design and Methods

Study site, field setting and duration of study

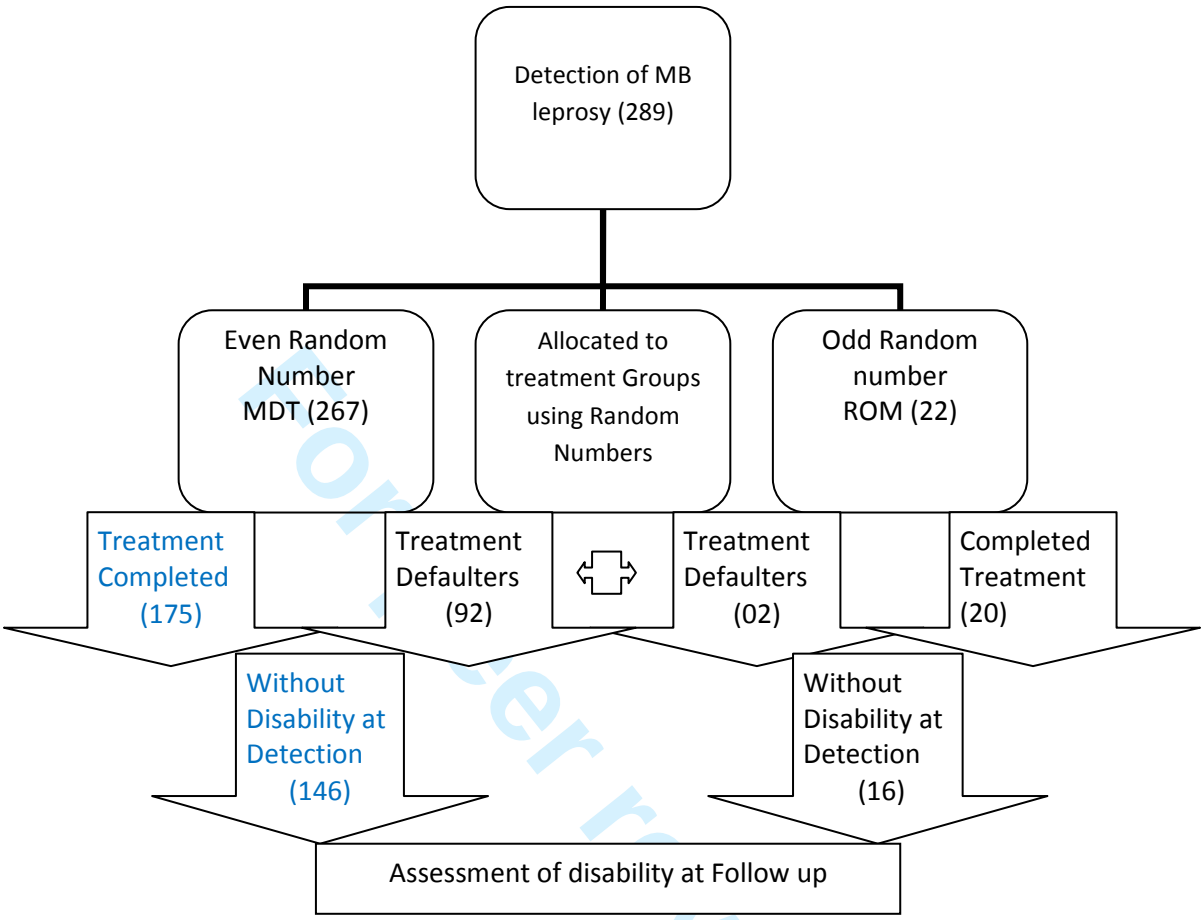
The study was started in our field area in Agra District of Uttar Pradesh on patients detected in field surveys under several studies on prevalence of leprosy during 2001-2006[3-6]. The Agra District is located 200 KM away from Delhi and spread in the radius of 100 KM on either side in length and borders with district Itawa & Firozabad on eastern side, Mathura & Bharatpur on north-west side and Gwalior & Dholpur on south side. Several studies were undertaken since the district was highly endemic for leprosy with prevalence of 16.4/10000 during 2001-03 and 7/10000 during 2004-06. The present study is based on patients detected in such surveys and all patients were followed up till April 2011.

Inclusion/Exclusion criterion of Patients for the study

Newly detected leprosy patients diagnosed clinically as multibacillary (MB) leprosy were taken for the study. This included patients with >5 skin lesions, either erythmatous or hypo-pigmented with definite impairment or loss of sensations (tested with ball point pen) or >2 thickened nerves. None of the patients had taken leprosy treatment earlier. Children below 5 and adults above 70 were although treated as per norms but not included in the study and so were the pregnant and lactating women.

Cohort size and treatment allocation and Assessment on Follow up

A total of 293 leprosy cases with multibacillary (MB) leprosy were detected. Of these 293, 4 patients did not start the treatment. The study was initially aimed to study the difference in the outcome of the two treatment arms (100 patients in each arm) i.e. Rifampicin 600mg, Ofloxacin 400 mg & Minocycline 200 mg (ROM) for adult and half of it for children (<15 years) as recommended by WHO vs. W.H.O. standard multidrug therapy (MDT: Rifampicin, Ofloxacin and Dapsone) given monthly for 12 months. Since W.H.O. suddenly withdrew ROM supply in 2003, only a small number of patients (22) were randomly (Using random number table) allocated to ROM arm by then and later on all the detected cases were put on MDT. Therefore, this study now aimed at studying risk of relapse and disability among MDT treated cases and ROM arm is not included. An attempt is also made to compare the risk of disability among those completed treatment as compared to those defaulted; either early (within 6 months) or late (during 6-11 months). All the cases that were started on treatment were followed up monthly till treatment completion, 6 monthly up to 3 years and then annually till the end of study. Disability Grade 1 was defined as patient developing anesthesia in palm or sole tested with a ball point pen and Grade 2 as visible deformity in either Hand or Feet or eye (Lagophthalmas). During this time, all cases of clinical relapse, reaction and developing of disability (Grade 1 & Grade 2) were recorded after medical confirmation and necessary medical relief was either provided or referred (see Flow chart).



Defining some parameters

A leprosy patient detected with leprosy related disability at the time of detection in the field survey was defined as **prevalence of disability**. The occurrence of disability detected at follow up in previously detected leprosy cases without disability at that time is define as **incidence of disability**. **Delay at detection or treatment** is the same i.e. duration of untreated disease as reported at first detection.

Ethical Approval and informed consent

Ethical Approval was taken from Institutional ethical committee who was being informed periodically about the progress of the work. All the patients were informed about the possible side effects, remedies and benefits. Although the treatment given was WHO standard regimen but for reasons of follow up etc patients were asked to consent and then they were put on respective treatment. In case of children, consent of their parents was taken.

Statistical methods

The comparison of patients developing disability was done using survival analysis and Log-Rank test to test the significance[7] using SPSS v12 software and Fisher exact test or χ^2 test of significance used to compare proportions[8]. The logistic regression analysis was done to undertake risk factor analysis.

Results

Demographic Characteristics of patients

The patients of all ages were detected in surveys. The mean age was 43.4 years (SEM=1.1) and median of 45 years. Most patients (69.3%) were aged 35 & above and only 6.4% were the child cases of MB leprosy. Male patients accounted for 61.0% of the total 267 cases in this study. At the time of survey, 25.1% patients were those who reported to acquire leprosy during last 12 months, 38.6% in last 12-36 months and rest had disease since over 36 months.

Prevalence of Disability at detection

The prevalence of grade 2 disability (visible) was found to be 10.1%. The prevalence of Grade 2 disability seems to rise slowly with increased age and male patients had higher disability (14.1 vs. 3.8, χ^2 = 7.4, p=0.007) than among the female patients. The Prevalence of disability also increased among patients who delayed treatment for longer period particularly beyond 36 months (χ^2 = 6.2, p=0.032), significantly high disability noted among patients with 3 or more thickened nerves (χ^2 = 7.3, p=0.026), and among patients with advance clinical stage of disease (BL/LL or Neuritic) (χ^2 = 37.9, p=0.000) than among those with disease of early stage (BT/BB). However, the prevalence of disability did not vary significantly among patients who defaulted from treatment than among those who completed treatment (χ^2 = 0.45, p=0.80) and by smear status (χ^2 = 4.6, p=0.10) . See Table 1.

Crude Incidence of disability (CID)

The crude incidence of disability is presented in Table 2. The crude incidence of disability (CID) was observed to be, 13.6% among treatment defaulters, higher than 10.5% among those completed treatment but not found significantly different (p>0.05) nor it had increased significantly by age of patients (p>0.05). Although the males had higher incidence of disability than in females (14.3 vs. 12.9 in defaulters and 12.9 vs. 6.6 in completed treatment group) but difference was not significant (p>0.05). The CID was found to be significantly high among MDT patients with neuritic leprosy (Patch 0) or with more than 10 patches (χ^2 = 15.0, p=0.002). The patients with 3 or more thicken nerves and still defaulted

had significantly higher disability developed (χ^2 = 7.7, p=0.021) in comparison to those patients on MDT who completed their treatment. Patients in MDT arm who had disease of high clinical spectrum like BL/LL/Neuritic leprosy were observed to have significantly high incidence of disability (χ^2=19.6, p<0.001). However, no difference was found by smear positivity status of patients.

Risk factors for prevalence of disability (pre-MDT stage)

Using logistic regression analysis, the attempt was made to assess the role of risk factors known to be responsible for causing disability. It was found that patients with 3 or more nerve involvement at the time of detection had 4.53 time risk of disability (OR=4.53, 95%CI: 1.54-13.4) presenting at detection and after adjusting the effect of age and delay in treatment, this showed (OR=3.73, 95%CI: 1.24-11.2). The second higher risk was found of the factor 'delay at detection" for treatment beyond 36 months i.e. (OR=2.27, 95%CI: 1.04-4.96) than among those who started treatment within 36 months of having disease- adjusted for age (Table 3).

Risk Factors for incidence of disability (post-MDT stage)

The risk of incidence of disability was assessed among those who were free from disability at the time detection. It is found that incidence of disability was high (OR=3.05, 95%CI: 1.10-8.48) among patients with 3 or more nerve involved and remained so (OR=2.81, 95%CI: 1.0-7.9) when standardized for age and delay in treatment (Table 4).

Incidence of disability

A detailed analysis on incidence of disability has been presented using survival analysis among different groups. The overall incidence of disability was found to be 2.74/100 person years with mean follow up of 4.28 years after treatment completion or from point of default (Table 5). The incidence of disability was 2.69/100 person years during a mean follow-up of 4.08 years in those patients completed MDT and 2.84/100 person years during a mean of 4.78 years after default (See Fig 1 & Fig.2).

The comparison of incidence (hazard) curve by years of follow up did not suggest significant difference between the two treatment groups, (Log Rank test =0.02, p=0.88).

A further analysis between early defaulters and late defaulters, although showed that early defaulters had highest incidence of disability (3.08/100 PY) than 2.3/100 PY in the group of late defaulters but

incidence curve over the years of follow up did not statistically differentiate (p>0.05) the two (See Figure 3 and 4).

Discussion

This study provide unique opportunity to assess the role of factors associated with prevalence of disability at case detection stage in active surveys and also the incidence of disability when patients with varying treatment status are followed up for years. The risk factors for the development of disability among MB patients appeared to be almost similar with increase nerve thickening (≥3 nerves) as number one risk factor and delay in treatment beyond 36 months as number 2 risk factor. A study conducted to assess the risk of paralytic deformity (Grade 2 & above) among cases detected in surveys had shown among patients with skin lesions who also had 3 -5 nerves, were found to have very high risk (OR=33.4) of deformity[9]. However, the patient of neuritic leprosy (No skin lesion) with delay in diagnosis for treatment of beyond 5 years had 17.5 times (OR) risk of developing deformity than among those with lesser delay[9].

The incidence of disability among these patients was found to be 2.74/100 person years of follow up; 2.69 in MDT arm and 2.84 in treatment defaulters with 33.9% (3.08 vs. 2.30) higher disability among early defaulters (3.08) and 2.30 among late defaulters. The study therefore clearly suggests that incidence of disability could only slightly be higher 6% (2.84 vs. 2.69) in the group completing required MDT than in those defaulting. The risk of disability in the present study was found higher than in Malawi study (5/1000 person years) [1]. The crude incidence of disability in this study was also high (10.5%) among those taken complete MDT treatment than 6.8% in South India Study[2] conducted during 1985-1992. However, the reasons for higher incidence of disability in this study are not clearly known.

Conclusion

The important conclusion of the study is that the initiation of treatment for leprosy is a must for reducing risk of incidence of disability and delay in initiating treatment would increase the risk of disability by many folds. Important is to note that incidence of disability between defaulters and those completing treatment is not found significantly different.

Contributors: Dr Anil Kumar was responsible for planning, conducting field study, analysis, writing; Dr Anita Girdhar for clinical evaluation and Dr. BK Girdhar for overall supervision, clinical monitoring and report preparation.

Statement of funding: This study was supported by an institutional grant from National JALMA Institute for Leprosy, Taj Ganj, Agra. No specific funding from external agencies was asked for.

Conflict of interests: None

Acknowledgement: Authors gratefully acknowledges the help extended by the institute by providing internal grant for the study. Thanks are also due to all patients who cooperated in the study and the paramedical workers and District leprosy officer for the support.

References

1. Ponnighaus IM, Boerrigter G, Fine PEM, et. Al.. Disabilities in leprosy patients ascertained in a total population survey in Karonga District, Northern Malawi. Lep Rev 1990; 61:366-374.
2. Selvaraj G, Prabhakar N, Muliyil J, et al. Incidence of disabilities among multibacillary cases after initiation of multidrug therapy and factors associated with the risk of developing disabilities. Ind J Lepr, 1998(suppl); 70:11S-16S.
3. Kumar A, Yadav VS, Girdhar A, et al. Some Epidemiological Observations on Leprosy in Agra, India. Int J Lepr **2001, 69(3):234-240.**
4. Kumar A, Girdhar A, Girdhar BK. Epidemiology of Leprosy in Urban Agra, India. Lepr Rev, 2003; 74:31-34.
5. Kumar A, Girdhar A, Girdhar BK. Prevalence of leprosy in Agra district (U.P.) India during 2001-2003. Int J Lepr ,2005, 73(2):115-121.
6. Kumar A, Girdhar A, Chakma JC, et al. A rapid survey for Leprosy in Agra District (2004-06): Epidemiological Observations. J Commun Dis; 2008,40(4): 277-284
7. Statistical Package for Social Sciences (SPSS) , version 12, 2006.
8. Le Chap T. Applied Catagorical data analysis, John wiley & Sons (USA) 1998.
9. Kumar A, Girdhar A, Girdhar BK. Nerve thickening in leprosy patients and risk of paralytic deformities: a field based study in Agra , India. Lepr Rev, 2004, 75:135-142.
10. Girdhar A, Kumar Anil, Girdhar B.K. A randomised controlled trial assessing the effect of adding clarithromycin to Rifampicin, ofloxacin and minocycline in the treatment of single lesion paucibacillary leprosy in Agra District, India. Lepr Rev, 2011, 82:1-10.

Table 1: Prevalence of Grade 2 disability at detection in MB leprosy patients by Demographic and Clinical status, Agra district (Uttar Pradesh) India during 2001-06

Charaecterstics		MDT Arm (267)	
		Cases	Percent Grade 2 Disability
Age	≤14	17	5.9
	15-24	25	4.0
	25-34	40	5.0
	35-54	108	13.9
	>54	77	10.4
Total		267	10.1
Mean (SEM)		43.4(1.1)	
Sex	Male	163	14.1
	Female	104	3.9
Delay in detection (months)	≤12	67	6.0
	13-36	103	8.7
	>36	97	14.4
Patches	0	12	50.0
1-5		16	25.0
6-10		84	3.6
>10		155	9.0
Nerves	0-2	99	4.0
	3-5	101	11.9
	>5	67	16.4
Clinical status			
BT/BTR		131	3.8
BB/BBR		74	5.4
BL/LL		51	25.5
N		11	45.5
Treatment status			
Defaulters		92	8.7
Completed		175	10.9
Smear	+ve	27	7.4
	-Ve	138	6.5
	Not done	102	15.7

Table 2: Crude incidence of disability (CID) by Demographic and Clinical status at Follow-up among multibacillary (MB) leprosy patients by treatment compliance status , Agra district (UP) India

	Completed Treatment		Defaulters		$\chi 2$ with p-value	
Charaecterstics	Cases	CID rate	Cases	CID rate	Completed Treatment	Defaulters
Age ≤14	12	0	2	0		
15-24	15	6.7	3	33.3		
25-34	30	9.7	9	0	>0.05	>0.05
35-54	64	15.6	25	12.0		
>54	41	7.3	20	20.0		
Total	162	10.5	59	13.6		
Sex Male	101	12.9	28	14.3	>0.05	>0.05
Female	61	6.6	31	12.9		
Delay in Treatment (months)						
≤12	44	6.8	14	7.1	>0.05	>0.05
13-36	63	11.1	26	11.5		
>36	55	12.7	19	21.1		
Patches						
0	5	60.0	0	0		
1-5	6	0	4	0	15.0,	>0.05
6-10	62	6.5	13	0	0.002	
>10	90	11.1	42	19.0		
Nerves						
0-2	66	4.8	28	7.1	>0.05	7.7,
3-5	60	11.7	17	5.9		0.021
>5	39	17.9	14	35.7		
Clinical status						
BT/BTR	94	4.3	24	8.3		
BB/BBR	38	13.2	23	21.7	19.6,	>0.05
BL/LL	25	20.0	12	8.3	<0.001	
N	5	60.0	0	0		
Smear						
-ve	101	8.9	28	17.9	>0.05	>0.05
+Ve	19	10.5	4	0		
Not done	42	14.3	27	11.1		

Table 3: Risk factors for Prevalence of disability at detection (Pre-MDT stage)			
	Odd Ratio (95%CI)	Odd Ratio (95%CI)	Odd Ratio (95%CI)
Nerves 0-2 3 or more	1.0 4.53(1.54-13.4)	1.0 3.87(1.30-11.6)	1.0 3.73(1.24-11.2)
Age <35 ≥35	--	1.0 2.49(0.83-7.50)	1.0 2.35(0.77-7.12)
Delay in treatment (mo) ≤36 >36	--	--	 1.0 2.27(1.04-4.96)
Standardized for	none	Age	Age & delay in treatment

Table 4: Risk factors for Incidence of disability post multidrug therapy			
	Odd Ratio (95%CI)	Odd Ratio (95%CI)	Odd Ratio (95%CI)
Nerves 0-2 3 or more	1.0 3.05(1.10-8.48)	1.0 2.84(1.01-8.0)	1.0 2.81(1.0-7.90)
Age <35 ≥35	--	1.0 1.63(0.57-4.58)	1.0 1.64(0.58-4.68)
Delay in treatment (mo) ≤36 >36	--	--	 1.0 1.22(0.57-2.61)
Standardized for	none	Age	Age & delay in treatment

Table 5: Incidence of disability /1000 Person years of follow up					
Treatment Group	Cases	Mean Years Survival Time	Persons Years (PY)	Disability developed in	Incidence/ 100 PY
Completed Treatment MDT	146	4.08	594.7	16	2.69
Defaulters of MDT Early (<6 months of Treatment) Late (6-11 month of Treatment)	59 38 21	4.78 5.12 4.14	281.9 194.9 87.0	08 06 02	2.84 3.08 2.30
All	205	4.28	876.6	24	2.74

Fig 1: Incidence of disability in MB leprosy patients who completed treatment

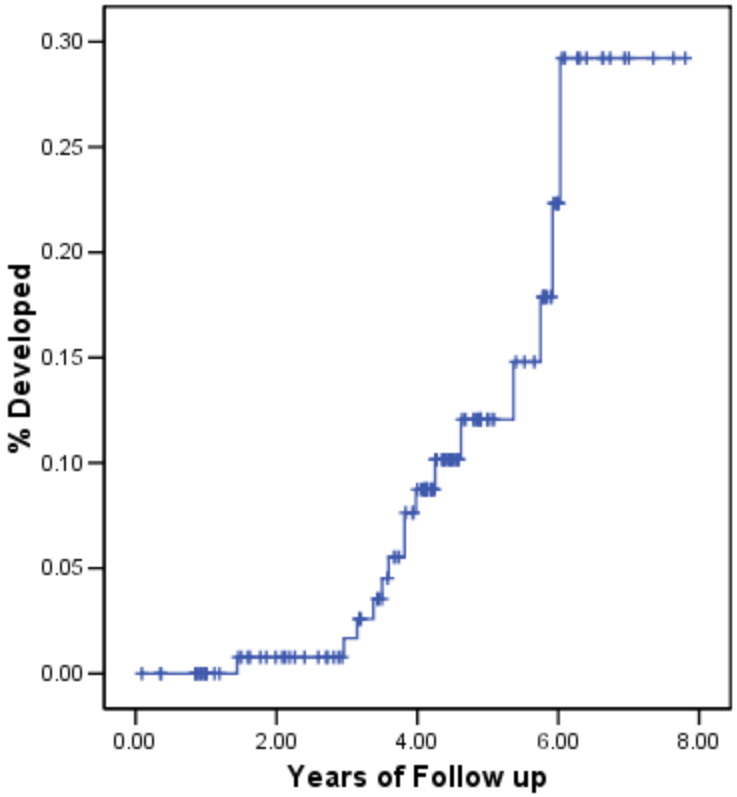


Figure 2: Risk of developing disability among MB leprosy patients post MDT by Treatment compliance

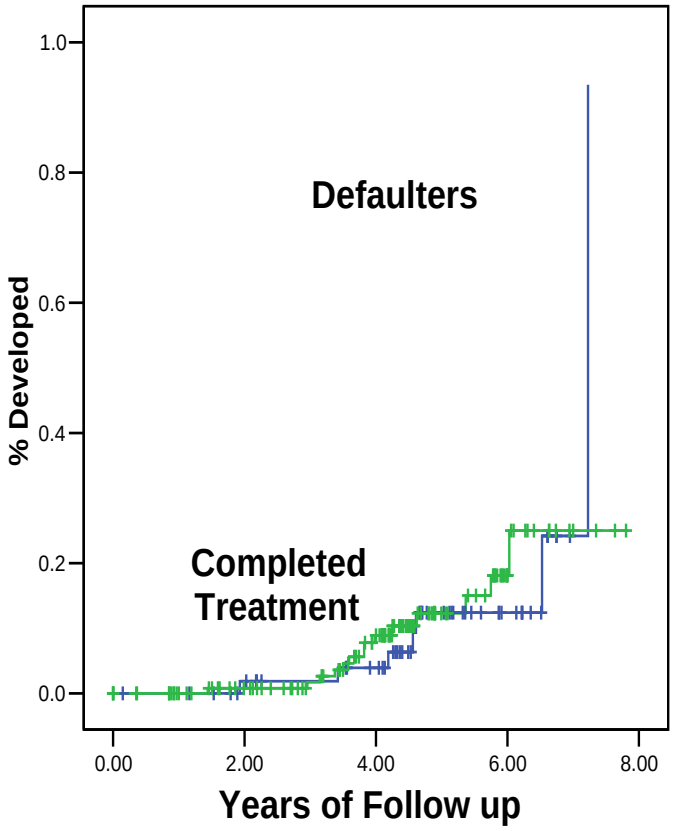


Figure 3: Risk of developing disability among MB leprosy patients post multidrug therapy

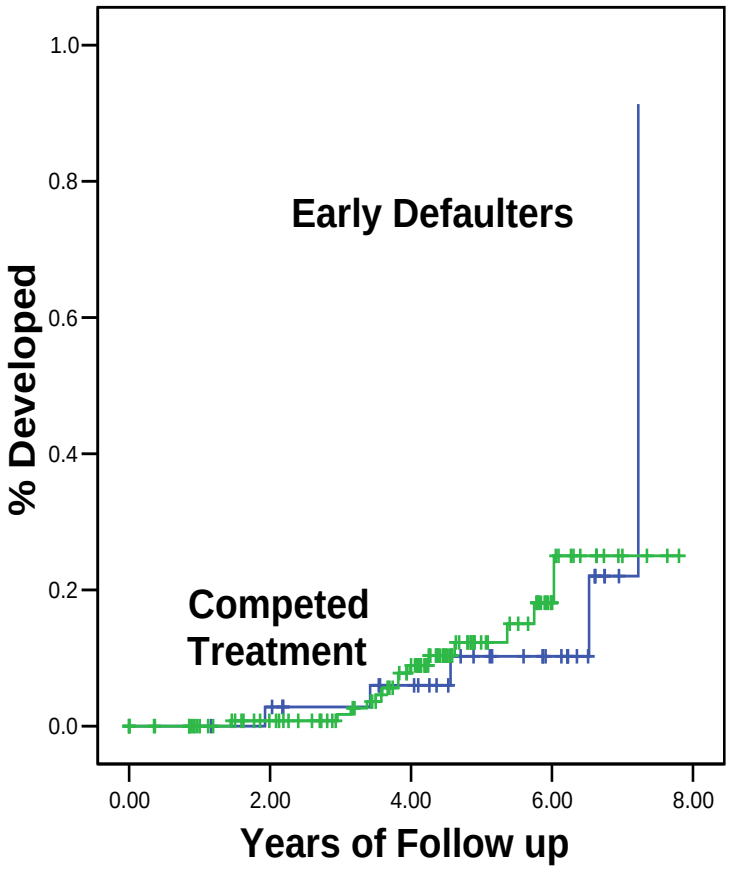
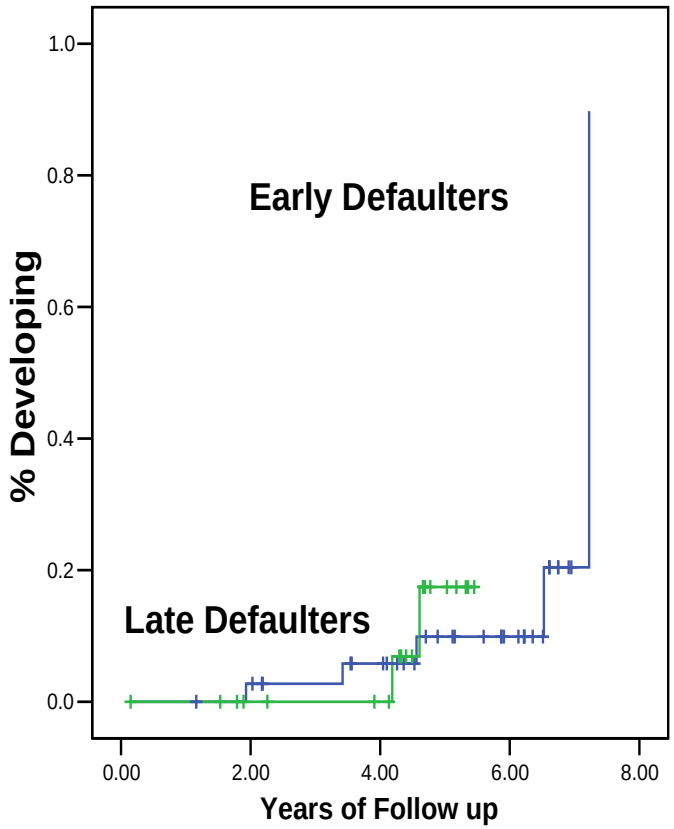


Figure 4: Risk of developing disability among MB leprosy patients who defaulted from MDT



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	5
		(c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	5-7
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Risk of disability in pre and post multidrug therapy (MDT) treatment among multibacillary leprosy- Agra MB cohort study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000361.R3
Article Type:	Research
Date Submitted by the Author:	10-Feb-2012
Complete List of Authors:	KUMAR, ANIL; National Institute for Leprosy & Other Mycobacterial Diseases, Biostatistics and Epidemiology GIRDHAR, ANITA; National Institute for Leprosy & Other Mycobacterial Diseases,, Clinical GIRDHAR, bhavneswar; National Institute for Leprosy & Other Mycobacterial Diseases,, Clinical
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Dermatology, Epidemiology, Evidence based practice, Health informatics, Health services research
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, CHEMOTHERAPY, INFECTIOUS DISEASES, EPIDEMIOLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Dermatopathology < PATHOLOGY

Risk of developing disability in pre and post multidrug therapy (MDT) treatment among multibacillary leprosy –Agra MB cohort study

Anil Kumar, Anita Girdhar, BK Girdhar

Epidemiology and Clinical Divisions, National JALMA Institute for Leprosy & Other Mycobacterial Diseases (ICMR), Taj Ganj, Agra (U.P.), India-282001

dranil250158@gmail.com

Abstract

Objectives: If Leprosy is a public health problem due to disabilities it causes. Surprisingly little is known about risk of disabilities. Even today, mainly cross-sectional studies reports disability prevalence. Present study aims to report risk of disability in pre and post WHO-MDT in multibacillary leprosy patients and to assess extent of incidence of disability.

Methods: The study design is prospective and setting is institutional field area. Patients detected during 2001-2006 field surveys. Of the 289 multibacillary patients, 146 completed study. Both sexes were involved. Primary outcome planned was to study cure of disease, relapses and disability in patients received MDT. Secondary outcome was to measure reaction and default. Assessment was done clinically. Data has been analyzed using SPSS software, Logistic, survival analysis was performed and χ^2 test of significance used.

Results: Important risk factor found is $\geq$3 nerves involved with odds of 3.73(1.24-11.2) and delay in treatment; 2.27(1.04-4.96) at pre-MDT stage and $\geq$3 nerves involved with odds of 2.81(1.0-7.9) at post-MDT stage. Incidence of disability was found to be 2.74/100 person years; 2.69 in MDT arm and 2.84 in defaulters with slightly higher disability among early defaulters (3.08) than 2.30 among late defaulters. The study suggests that incidence of disability could be slightly higher if treatment is not completed.

Conclusion: Early treatment for leprosy is a must for reducing risk of disability and treatment delay would increase the risk of disability. Important is to note that incidence of disability between defaulters and those completed treatment is not found significantly different.

Introduction

If Leprosy is a public health problem, it is due to the disabilities it causes. It was surprising to note that this being so important, very little was known about the risk of disabilities[1] and even today there is mainly cross sectional studies at population level which reports disability prevalence among leprosy patients. The prevalence of disability however varies significantly from one study to another. In Malawi study, disability prevalence varied from 20% to 10% during 1973 to 1987[1]. The studies done in India[2-6] reported visible deformities rate from 2.8% to 24.3% among cases at registration or detection in population surveys. However a very few studies on risk of developing disabilities have been undertaken. Although Malawi study[1] had reported risk of developing disabilities as 5/1000 Person years during pre-MDT era and South India study[2] observed disability rate of 6.8% but this was a crude estimate without referring to time. The risk of developing disabilities is also very important for the national programme on prevention of disabilities.

This study was therefore attempted to assess the risk/incidence of developing disability among those leprosy patients who had no disability at the time of detection in field surveys but developed it during the years of follow up after completion of W.H.O. multidrug treatment (MDT).

Design and Methods

Study site, field setting and duration of study

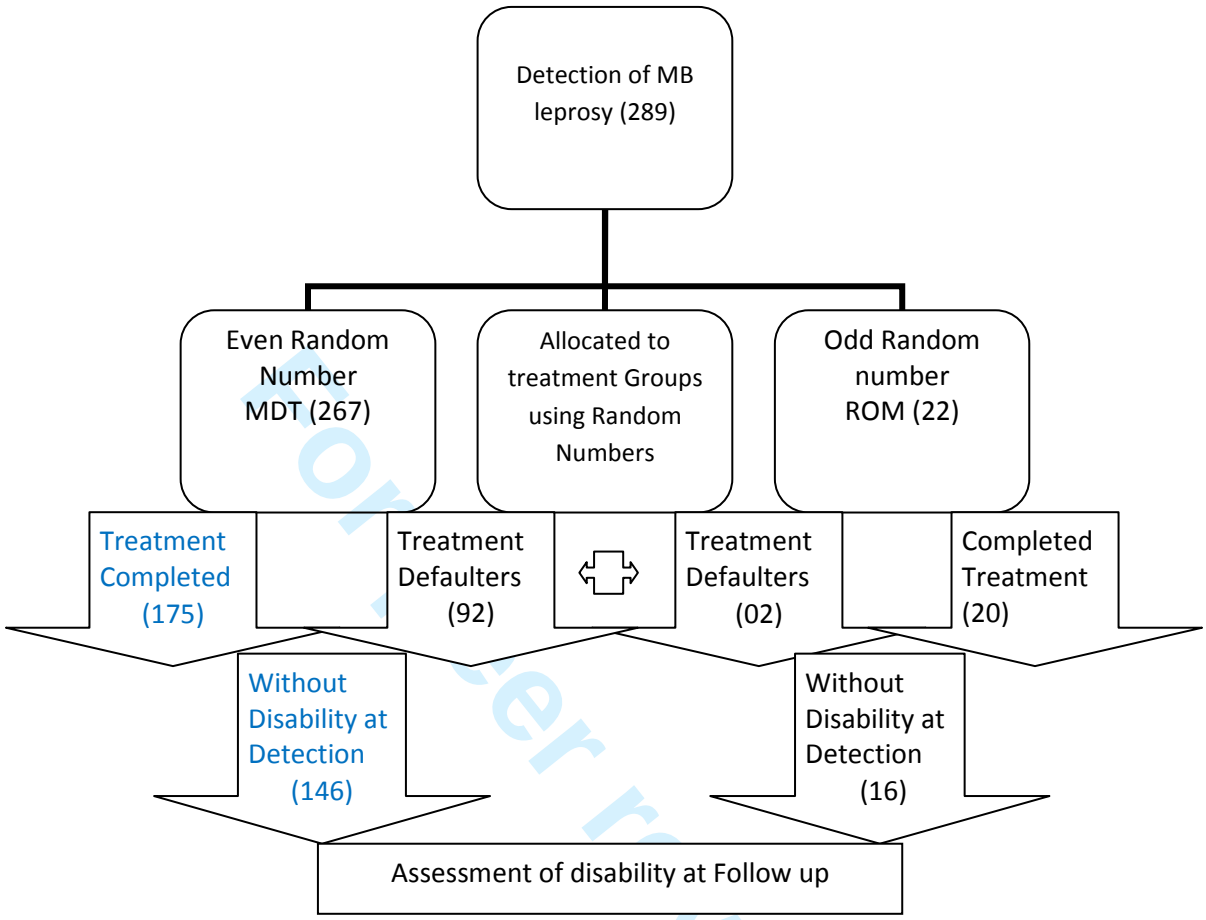
The study was started in our field area in Agra District of Uttar Pradesh on patients detected in field surveys under several studies on prevalence of leprosy during 2001-2006[3-6]. The Agra District is located 200 KM away from Delhi and spread in the radius of 100 KM on either side in length and borders with district Itawa & Firozabad on eastern side, Mathura & Bharatpur on north-west side and Gwalior & Dholpur on south side. Several studies were undertaken since the district was highly endemic for leprosy with prevalence of 16.4/10000 during 2001-03 and 7/10000 during 2004-06. The present study is based on patients detected in such surveys and all patients were followed up till April 2011.

Inclusion/Exclusion criterion of Patients for the study

Newly detected leprosy patients diagnosed clinically as multibacillary (MB) leprosy were taken for the study. This included patients with >5 skin lesions, either erythmatous or hypo-pigmented with definite impairment or loss of sensations (tested with ball point pen) or >2 thickened nerves. None of the patients had taken leprosy treatment earlier. Children below 5 and adults above 70 were although treated as per norms but not included in the study and so were the pregnant and lactating women.

Cohort size and treatment allocation and Assessment on Follow up

A total of 293 leprosy cases with multibacillary (MB) leprosy were detected. Of these 293, 4 patients did not start the treatment. The study was initially aimed to study the difference in the outcome of the two treatment arms (100 patients in each arm) i.e. Rifampicin 600mg, Ofloxacin 400 mg & Minocycline 200 mg (ROM) for adult and half of it for children (<15 years) as recommended by WHO vs. W.H.O. standard multidrug therapy (MDT: Rifampicin, Ofloxacin and Dapsone) given monthly for 12 months. Since W.H.O. suddenly withdrew ROM supply in 2003, only a small number of patients (22) were randomly (Using random number table) allocated to ROM arm by then and later on all the detected cases were put on MDT. Therefore, this study now aimed at studying risk of relapse and disability among MDT treated cases and ROM arm is not included in this study. An attempt is also made to compare the risk of disability among those completed treatment as compared to those defaulted; either early (within 6 months) or late (during 6-11 months). All the cases that were started on treatment were followed up monthly till treatment completion, 6 monthly up to 3 years and then annually till the end of study. Disability Grade 1 was defined as patient developing anesthesia in palm or sole tested with a ball point pen and Grade 2 as visible deformity in either Hand or Feet or eye (Lagophthalmas). During this time, all cases of clinical relapse, reaction and developing of disability (Grade 1 & Grade 2) were recorded after medical confirmation and necessary medical relief was either provided or referred (see Flow chart).



Defining some parameters

A leprosy patient detected with leprosy related disability at the time of detection in the field survey was defined as **prevalence of disability**. The occurrence of disability detected at follow up in previously detected leprosy cases without disability at that time is define as **incidence of disability**. **Delay at detection or treatment** is the same i.e. duration of untreated disease as reported at first detection.

Ethical Approval and informed consent

Ethical Approval was taken from Institutional ethical committee who was being informed periodically about the progress of the work. All the patients were informed about the possible side effects, remedies and benefits. Although the treatment given was WHO standard regimen but for reasons of follow up etc, the patients were asked to consent and then they were put on respective treatment. In case of children, consent of their parents was taken.

Statistical methods

The comparison of patients developing disability was done using survival analysis and Log-Rank test to test the significance[7] using SPSS v12 software and Fisher exact test or χ^2 test of significance used to compare proportions[8]. The logistic regression analysis was done to undertake risk factor analysis.

Results

Demographic Characteristics of patients

The patients of all ages were detected in surveys. The mean age was 43.4 years (SEM=1.1) and median of 45 years. Most patients (69.3%) were aged 35 & above and only 6.4% were the child cases. Male patients in this study accounted for 61.0% of the total 267 cases put on MB-MDT. At the time of survey, 25.1% patients were those who reported to acquire leprosy during last 12 months, 38.6% in last 12-36 months and rest had disease since over 36 months.

Prevalence of Disability at detection

The prevalence of grade 2 disability (visible) was found to be 10.1%. The prevalence of Grade 2 disability seems to rise slowly with increased age and male patients had higher disability (14.1 vs. 3.8, χ^2 = 7.4, p=0.007) than among the female patients. The Prevalence of disability also increased among patients who delayed treatment for longer period particularly beyond 36 months (χ^2 = 6.2, p=0.032). Significantly high disability was noted among patients with 3 or more thickened nerves (χ^2 = 7.3, p=0.026), and among patients with advance clinical stage of disease (BL/LL or Neuritic) (χ^2 = 37.9, p=0.000) than among those with disease of early stage (BT/BB). However, the prevalence of disability did not vary significantly among patients who defaulted from treatment than among those who completed treatment (χ^2 = 0.45, p=0.80) and by smear status (χ^2 = 4.6, p=0.10). See Table 1.

Crude Incidence of disability (CID)

The crude incidence of disability is presented in Table 2. The crude incidence of disability (CID) was observed to be, 13.6% among treatment defaulters, higher than 10.5% among those completed treatment but not found significantly different (p>0.05) nor it had increased significantly by age of patients (p>0.05). Although the males had higher incidence of disability than in females (14.3 vs. 12.9 in defaulters and 12.9 vs. 6.6 in completed treatment group) but difference was not significant (p>0.05). The CID was found to be significantly high among MDT patients with neuritic leprosy (Patch 0) or with more than 10 patches (χ^2 = 15.0, p=0.002). The patients with 3 or more thicken nerves and still defaulted

had significantly higher disability developed (χ^2 = 7.7, p=0.021) in comparison to those patients on MDT who completed their treatment. Patients in MDT arm who had disease of high clinical spectrum like BL/LL/Neuritic leprosy were observed to have significantly high incidence of disability (χ^2=19.6, p<0.001). However, no difference was found by smear positivity status of patients.

Risk factors for prevalence of disability (pre-MDT stage)

Using logistic regression analysis, the attempt was made to assess the role of risk factors known to be responsible for causing disability. It was found that patients with 3 or more nerve involvement had 4.53 time higher risk of disability (OR=4.53, 95%CI: 1.54-13.4) presenting at detection and after adjusting the effect of age and delay in treatment, this showed (OR=3.73, 95%CI: 1.24-11.2) than in others. The second higher risk was found of the factor 'delay at detection" for treatment beyond 36 months i.e. (OR=2.27, 95%CI: 1.04-4.96) than among those who started treatment within 36 months of having disease- adjusted for age (Table 3).

Risk Factors for incidence of disability (post-MDT stage)

The risk of incidence of disability was assessed among those who were free from disability at the time detection. It is found that incidence of disability was high (OR=3.05, 95%CI: 1.10-8.48) among patients with 3 or more nerve involved and remained so (OR=2.81, 95%CI: 1.0-7.9) when standardized for age and delay in treatment (Table 4).

Incidence of disability

A detailed analysis on incidence of disability has been presented using survival analysis among different groups. The overall incidence of disability was found to be 2.74/100 person years with mean follow up of 4.28 years after treatment completion or from point of default (Table 5). The incidence of disability was 2.69/100 person years during a mean follow-up of 4.08 years in those patients completed MDT and 2.84/100 person years during a mean of 4.78 years after default (See Fig 1 & Fig.2).

The comparison of incidence (hazard) curve by years of follow up did not suggest significant difference between the two treatment groups, (Log Rank test =0.02, p=0.88).

A further analysis between early defaulters and late defaulters, although showed that early defaulters had highest incidence of disability (3.08/100 PY) than 2.3/100 PY in the group of late defaulters but

incidence curve over the years of follow up did not statistically differentiate (p>0.05) the two (See Figure 3 and 4).

Discussion

This study provide unique opportunity to assess the role of factors associated with prevalence of disability at case detection stage in active surveys and also the incidence of disability when patients with varying treatment status are followed up for years. The risk factors for the development of disability among MB patients appeared to be almost similar with increase nerve thickening (≥3 nerves) as number one risk factor and delay in treatment beyond 36 months as number 2 risk factor. A study conducted to assess the risk of paralytic deformity (Grade 2 & above) among cases detected in surveys had shown among patients with skin lesions who also had 3 -5 nerves, were found to have very high risk (OR=33.4) of deformity[9]. However, the patient of neuritic leprosy (No skin lesion) with delay in diagnosis for treatment of beyond 5 years had 17.5 times (OR) risk of developing deformity than among those with lesser delay[9].

The incidence of disability among these patients was found to be 2.74/100 person years of follow up; 2.69 in MDT arm and 2.84 in treatment defaulters with 33.9% (3.08 vs. 2.30) higher disability among early defaulters (3.08) and 2.30 among late defaulters. The study therefore clearly suggests that incidence of disability could only slightly be higher 6% (2.84 vs. 2.69) in the group completing required MDT than in those defaulting. The risk of disability in the present study was found higher than in Malawi study (5/1000 person years) [1]. The crude incidence of disability in this study was also high (10.5%) among those taken complete MDT treatment than 6.8% in South India Study[2] conducted during 1985-1992. However, the reasons for higher incidence of disability in this study are not clearly known. One of the possible reasons could be that pathways for disabilities are set in before the treatment started and thus occurrence of disability could not b interfered. Secondly, once the disease affects an individual, the treatment may not be able to prevent disability. However, in the absence of proper studies, these are just possibilities.

Conclusion

The important conclusion of the study is that the initiation of treatment for leprosy is a must for reducing risk of incidence of disability and delay in initiating treatment would increase the risk of

disability by many folds. Important is to note that incidence of disability between defaulters and those completing treatment is not found significantly different.

Contributors: Although all the authors were responsible for conception, design and acquisition of data, drafting , revising and final approval of the article but Dr Anil Kumar played lead role in planning, conducting field study, analysis, writing revision and submission; Dr Anita Girdhar for clinical evaluation and Dr. BK Girdhar for clinical monitoring and report preparation.

Statement of funding: This study was supported by an institutional grant from National JALMA Institute for Leprosy, Taj Ganj, Agra. No specific funding from external agencies was asked for.

Conflict of interests: None

Data Sharing: No extra data

Acknowledgement: Authors gratefully acknowledges the help extended by the institute by providing internal grant for the study. Thanks are also due to all patients who cooperated in the study and the paramedical workers and District leprosy officer for the support.

References

1. Ponnighaus IM, Boerrigter G, Fine PEM, et. al... Disabilities in leprosy patients ascertained in a total population survey in Karonga District, Northern Malawi. Lep Rev 1990; 61:366-374.
2. Selvaraj G, Prabhakar N, Muliyil J, et al. Incidence of disabilities among multibacillary cases after initiation of multidrug therapy and factors associated with the risk of developing disabilities. Ind J Lepr, 1998(suppl); 70:11S-16S.
3. Kumar A, Yadav VS, Girdhar A, et al. Some Epidemiological Observations on Leprosy in Agra, India. Int J Lepr **2001, 69(3):234-240.**
4. Kumar A, Girdhar A, Girdhar BK. Epidemiology of Leprosy in Urban Agra, India. Lepr Rev, 2003; 74:31-34.
5. Kumar A, Girdhar A, Girdhar BK. Prevalence of leprosy in Agra district (U.P.) India during 2001-2003. Int J Lepr ,2005, 73(2):115-121.
6. Kumar A, Girdhar A, Chakma JC, et al. A rapid survey for Leprosy in Agra District (2004-06): Epidemiological Observations. J Commun Dis; 2008,40(4): 277-284
7. Statistical Package for Social Sciences (SPSS) , version 12, 2006.
8. Le Chap T. Applied Catagorical data analysis, John wiley & Sons (USA) 1998.
9. Kumar A, Girdhar A, Girdhar BK. Nerve thickening in leprosy patients and risk of paralytic deformities: a field based study in Agra , India. Lepr Rev, 2004, 75:135-142.

Table 1: Prevalence of Grade 2 disability at detection in MB leprosy patients by Demographic and Clinical status, Agra district (Uttar Pradesh) India during 2001-06

Charaecterstics		MDT Arm (267)	
		Cases	Percent Grade 2 Disability
Age	≤14	17	5.9
	15-24	25	4.0
	25-34	40	5.0
	35-54	108	13.9
	>54	77	10.4
Total		267	10.1
Mean (SEM)		43.4(1.1)	
Sex	Male	163	14.1
	Female	104	3.9
Delay in detection (months)	≤12	67	6.0
	13-36	103	8.7
	>36	97	14.4
Patches	0	12	50.0
	1-5	16	25.0
	6-10	84	3.6
	>10	155	9.0
Nerves	0-2	99	4.0
	3-5	101	11.9
	>5	67	16.4
Clinical status			
BT/BTR		131	3.8
BB/BBR		74	5.4
BL/LL		51	25.5
N		11	45.5
Treatment status			
Defaulters		92	8.7
Completed		175	10.9
Smear	+ve	27	7.4
	-Ve	138	6.5
	Not done	102	15.7

Table 2: Crude incidence of disability (CID) by Demographic and Clinical status at Follow-up among multibacillary (MB) leprosy patients by treatment compliance status , Agra district (UP) India

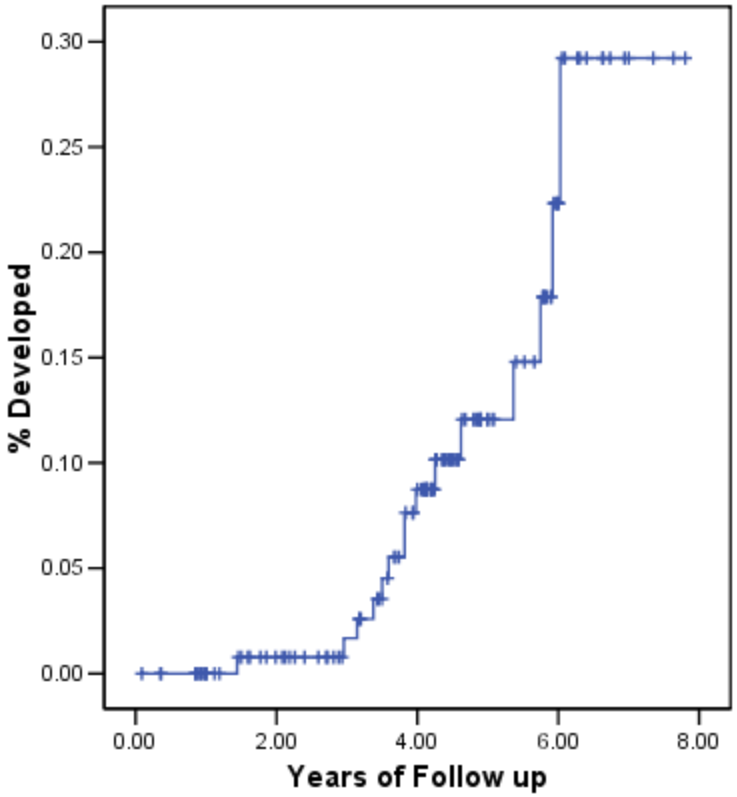
	Completed Treatment		Defaulters		χ2 with p-value	
Charaecterstics	Cases	CID rate	Cases	CID rate	Completed Treatment	Defaulters
Age ≤14	12	0	2	0		
15-24	15	6.7	3	33.3		
25-34	30	9.7	9	0	>0.05	>0.05
35-54	64	15.6	25	12.0		
>54	41	7.3	20	20.0		
Total	162	10.5	59	13.6		
Sex Male	101	12.9	28	14.3	>0.05	>0.05
Female	61	6.6	31	12.9		
Delay in Treatment (months)						
≤12	44	6.8	14	7.1	>0.05	>0.05
13-36	63	11.1	26	11.5		
>36	55	12.7	19	21.1		
Patches						
0	5	60.0	0	0		
1-5	6	0	4	0	15.0,	>0.05
6-10	62	6.5	13	0	0.002	
>10	90	11.1	42	19.0		
Nerves						
0-2	66	4.8	28	7.1	>0.05	7.7,
3-5	60	11.7	17	5.9		0.021
>5	39	17.9	14	35.7		
Clinical status						
BT/BTR	94	4.3	24	8.3		
BB/BBR	38	13.2	23	21.7	19.6,	>0.05
BL/LL	25	20.0	12	8.3	<0.001	
N	5	60.0	0	0		
Smear						
-ve	101	8.9	28	17.9	>0.05	>0.05
+Ve	19	10.5	4	0		
Not done	42	14.3	27	11.1		

Table 3: Risk factors for Prevalence of disability at detection (Pre-MDT stage)			
	Odd Ratio (95%CI)	Odd Ratio (95%CI)	Odd Ratio (95%CI)
Nerves 0-2 3 or more	1.0 4.53(1.54-13.4)	1.0 3.87(1.30-11.6)	1.0 3.73(1.24-11.2)
Age <35 ≥35	--	1.0 2.49(0.83-7.50)	1.0 2.35(0.77-7.12)
Delay in treatment (mo) ≤36 >36	--	--	 1.0 2.27(1.04-4.96)
Standardized for	none	Age	Age & delay in treatment

Table 4: Risk factors for Incidence of disability post multidrug therapy			
	Odd Ratio (95%CI)	Odd Ratio (95%CI)	Odd Ratio (95%CI)
Nerves 0-2 3 or more	1.0 3.05(1.10-8.48)	1.0 2.84(1.01-8.0)	1.0 2.81(1.0-7.90)
Age <35 ≥35	--	1.0 1.63(0.57-4.58)	1.0 1.64(0.58-4.68)
Delay in treatment (mo) ≤36 >36	--	--	 1.0 1.22(0.57-2.61)
Standardized for	none	Age	Age & delay in treatment

Table 5: Incidence of disability /1000 Person years of follow up					
Treatment Group	Cases	Mean Years Survival Time	Persons Years (PY)	Disability developed in	Incidence/ 100 PY
Completed Treatment MDT	146	4.08	594.7	16	2.69
Defaulters of MDT	59	4.78	281.9	08	2.84
Early (<6 months of Treatment)	38	5.12	194.9	06	3.08
Late (6-11 month of Treatment)	21	4.14	87.0	02	2.30
All	205	4.28	876.6	24	2.74

Fig 1: Incidence of disability in MB leprosy patients who completed treatment



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	5
		(c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	18	Summarise key results with reference to study objectives	5-7
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-8
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Figure 2: Risk of developing disability among MB leprosy patients post MDT by Treatment compliance

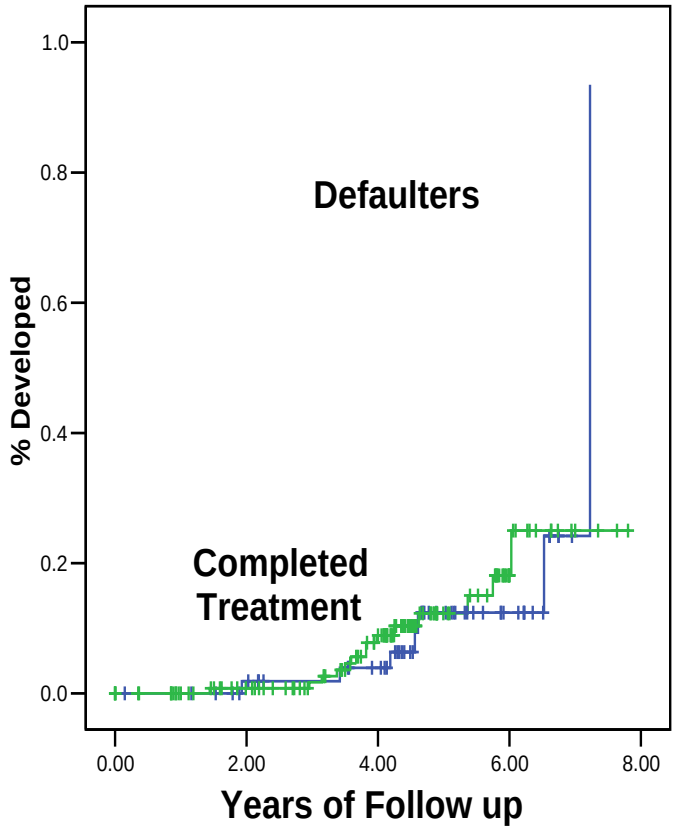


Figure 3: Risk of developing disability among MB leprosy patients post multidrug therapy

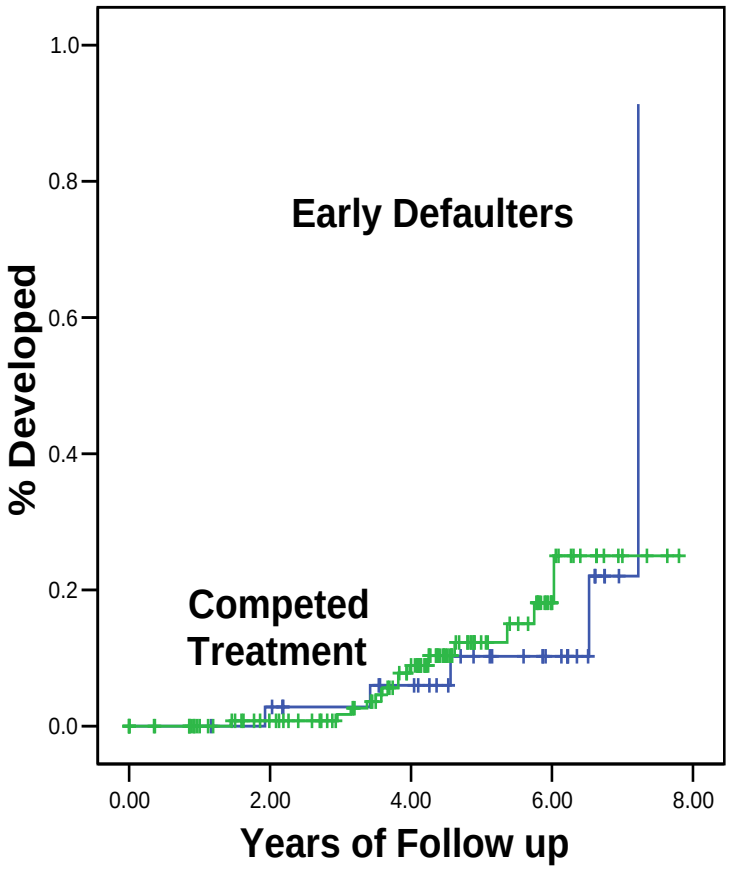


Figure 4: Risk of developing disability among MB leprosy patients who defaulted from MDT