PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of disability in pre and post multidrug therapy (MDT) treatment among multibacillary leprosy- Agra MB cohort study
AUTHORS	Anil Kumar, Anita Girdhar and BK Girdhar

VERSION 1 - REVIEW

REVIEWER	Dr. Maninder Singh Setia, MD PhD MPH Consultant Dermatologist and Epidemiologist Mumbai - India
REVIEW RETURNED	18/10/2011

REPORTING & ETHICS	Ethics approval not mentioned in the paper.
GENERAL COMMENTS	Abstract: Leprosy 'is' rather than 'was' in the first sentence Methodology: The study methods have been inadequately described. Was the study conducted in the period 2001-2006 or the cases that were detected in this time period included for the study till 2011 What dose of ROM was used? Single dose or multiple doses for MDT? Are there any WHO recommendations for MB leprosy? This is important to know the follow-up period The method of allocation of ROM and MDT is not necessarily random. You should state the exact method – i.e odd number of patient examined/enrolled etc. Ethical approval: Was an ethical approval obtained? Even if it is secondary data (which I don't think is the case in your study) please mention about the ethical approval – who provided it? Results There is no description of the population e.g. demographics etc. It will be useful to start the results section with this information. You have presented in the table, atleast put a sentence to that effect in the beginning of the results section. You talk about delayed treatment – how was it defined in your study? Under the Crude Incidence of Disability You mention that the percentages were significantly different, yet your p value is > 0.05. It should probably be p<0.05.. You talk about neuritic leprosy in results, however it is not mentioned in the methods section Page 6: The sentence "The CID was found to be significantly high……….treatment" is confusing. Please redraft the sentence and have shorter sentences Under Risk Factors for prevalence of disability at detection, you

| | have started by saying "Using logistic regression methods…" however, this type of analysis has not even been mentioned in the methods section.

Tables; Please provide elaborate titles for tables.
You have checked all the items in Strobe's checklist; however, those have not been adequately described in the text. Please clarify all the predictors and outcomes in methods section
All the statistical methods have not been described.

Figures:
In figure 1 your title is "Risk of developing disability in MB patients after MDT therapy". But the graph also shown ROM therapy. Please modify the title or the graph. In general, this is a useful study; however it is limited by inadequate information in methods section. |
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| **REVIEWER** | Bishwa Raj Sapkota
Anandaban Hospital,, Mycobacterial Research Laboratory
No competing interests |
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| **REVIEW RETURNED** | 24/11/2011 |

| **GENERAL COMMENTS** | Overall, the manuscript is well-written, although inclusion of some further details would facilitate reading and provide greater comprehension. To make it more inclusive considering to the target audiences, following recommendations have been made:
- The precise treatment regime of MDT and ROM should be provided
- A brief explanation on the setting of field survey would aid in understanding the coverage area and study site in details. Page 4 | 34 – statement of 'several active field surveys were undertaken' is vague, requires further clarification.
- Define the diagnosis criteria used to define the cases. Describe in details about the inclusion and exclusion criteria used. Describe the potential bias and any efforts to address these. Please clarifies how the assessments of the anesthesia in palm or sole were assessed?
- Bacterial index and reaction are also the critical variables for the risk of disability and impairment. Type 1 reaction is one of the major causes of nerve damage in leprosy patients leading to disabilities of varying severity. Although, the authors have mention about the relapse and reaction in the text (including abstract), however, the analysis and further details on these parameters are completely lacking in the manuscript.
- Page 5: Flowchart is too messy, please do consider in presenting in simpler form.
- Page 8 | 29 -35: Multiple factors are associated with the outcome, so the saying of 'ineffectiveness of therapy' is too strong and hyperbolic. Please discuss these parameters with citation.
- References: Please check the consistency in reference style
- No mention of approval by ethical review board (IRB) and consenting of participants.
- Table: Please provide the details of the abbreviation used in table. |
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Dr. Maninder Singh Setia, MD PhD MPH
Consultant Dermatologist and Epidemiologist, Mumbai - India

Abstract: Leprosy 'is' rather than 'was' in the first sentence   Corrected

Methodology: The study methods have been inadequately described.   Done

Was the study conducted in the period 2001-2006 or the cases that were detected in this time period included for the study till 2011

What dose of ROM was used? Single dose or multiple doses for MDT? Are there any WHO recommendations for MB leprosy? This is important to know the follow-up period

The method of allocation of ROM and MDT is not necessarily random. You should state the exact method – i.e odd number of patient examined/enrolled etc. (Random number from random number table –odd number was given to one arm and even to another- clarified in methods section)

Ethical approval: Was an ethical approval obtained? Even if it is secondary data (which I don't think is the case in your study) please mention about the ethical approval – who provided it? (Added)

Results

There is no description of the population e.g. demographics etc. It will be useful to start the results section with this information. You have presented in the table, atleast put a sentence to that effect in the beginning of the results section.   (Added)

You talk about delayed treatment – how was it defined in your study? (Delay is defined in seeking treatment from the first observation on skin lesion)

Under the Crude Incidence of Disability

You mention that the percentages were significantly different, yet your p value is > 0.05. It should probably be p<0.05..   (The statement included 'nor' and is correct)

You talk about neuritic leprosy in results, however it is not mentioned in the methods section

Page 6: The sentence "The CID was found to be significantly high……….treatment" is confusing. Please redraft the sentence and have shorter sentences   (Done)

Under Risk Factors for prevalence of disability at detection, you have started by saying "Using logistic regression methods…" however, this type of analysis has not even been mentioned in the methods section.   (Included)

Tables; Please provide elaborate titles for tables.   (Attempted)

You have checked all the items in Strobe's checklist; however, those have not been adequately described in the text. Please clarify all the predictors and outcomes in methods section

All the statistical methods have not been described.

Figures:

In figure 1 your title is "Risk of developing disability in MB patients after MDT therapy". But the graph also shown ROM therapy. Please modify the title or the graph. (Since ROM & MDT both are multidrug treatments , the title seems alright)

In general, this is a useful study; however it is limited by inadequate information in methods section. (Hopefully all the points are taken into consideration and necessary inclusions are done)

Reviewer 2: Bishwa Raj Sapkota
Anandaban Hospital, Mycobacterial Research Laboratory
No competing interests

Overall, the manuscript is well-written, although inclusion of some further details would facilitate reading and provide greater comprehension. To make it more inclusive considering to the target audiences, following recommendations have been made:

- The precise treatment regime of MDT and ROM should be provided (Done)

- A brief explanation on the setting of field survey would aid in understanding the coverage area and

study site in details. Page 4 | 34 – statement of 'several active field surveys were undertaken' is vague, requires further clarification. (Details provided)

- Define the diagnosis criteria used to define the cases. Describe in details about the inclusion and exclusion criteria used. Describe the potential bias and any efforts to address these. Please clarifies how the assessments of the anesthesia in palm or sole were assessed?   (Provided)

- Bacterial index and reaction are also the critical variables for the risk of disability and impairment. Type 1 reaction is one of the major causes of nerve damage in leprosy patients leading to disabilities of varying severity. Although, the authors have mention about the relapse and reaction in the text (including abstract), however, the analysis and further details on these parameters are completely lacking in the manuscript. (It is true that high BI and reaction but of severe type 2 do cause high disability. However in this study, 3 reactions were reported and 1 developed disability as observed in followup. One of the reason of low disability in reaction cases could be low since all were attended early and necessary steroid doze was provided. A separate paper is being prepared on relapse and reaction. This paper was centred on disability only).

- Page 5: Flowchart is too messy, please do consider in presenting in simpler form.
                                    (Attempted to simplify)
- Page 8 | 29 -35: Multiple factors are associated with the outcome, so the saying of 'ineffectiveness of therapy' is too strong and hyperbolic. Please discuss these parameters with citation.
                                        (This is just the possibility and its evidence comes from relapses. The paper on this data reveals rlapse rate 2/100 person years)
- References: Please check the consistency in reference style

- No mention of approval by ethical review board (IRB) and consenting of participants. (Paragraph added in method section)

- Table: Please provide the details of the abbreviation used in table. (provided)

VERSION 2 – REVIEW

REVIEWER	Dr. Maninder Singh Setia, MD, PhD, MPH Consultant Dermatologist and Epidemiologist, Mumbai - India
REVIEW RETURNED	02/01/2012

THE STUDY	The research question, the outcome, and the results have to match. There seems to be some incosistencies
RESULTS & CONCLUSIONS	The results have to be according to the research question
GENERAL COMMENTS	Comments This is an important paper and has good information. I have the following comments Introduction: It seems too didactic. The authors have highlighted study after study. One tends to get lost in so many studies. I would encourage them to summarise all the studies and add their comments, so as to lead the readers to a research question and hypothesis Methods Please define the outcome more clearly – what is measured in prevalence of disability and what is measured in incidence of disability. Also, please specify the explanatory variables – how did you

	measure delay in treatment? How did you measure delay in detection? Results All the results are presented. I am still not sure as to what is the main research question – According to the introduction it is to assess the risk…….. WHO MDT treatment. However, in methods and results they introduce ROM. They provide some explanation in the methods section. However, I would strongly urge them to be consistent. One seems to get lost in the results and discussion section. Please modify the manuscript accordingly.

REVIEWER	Bishwa Raj Sapkota Anandaban Hospital,, Mycobacterial Research Laboratory No competing interests
REVIEW RETURNED	11/01/2012

The reviewer filled out the checklist but made no further comment.

VERSION 2 – AUTHOR RESPONSE

ROM component is now deleted and whole analysis concentrates on MDT results.
English grammer check is done and now it should satisfies both the referees. A paragraph explaing prevalence, incidence and delay in detection or treatment is added in method section.

VERSION 3 – REVIEW

REVIEWER	Dr. Maninder Singh Setia, MD, PhD, MPH Consultant Dermatologist and Epidemiologist, Mumbai - India
REVIEW RETURNED	04/02/2012

RESULTS & CONCLUSIONS	Though the authors have cleared the issue - they have removed ROM group, some of the sentences still maintain the complete sample and MDT group - Please change that.
GENERAL COMMENTS	You could have elaborated the discussion a bit more. It more or less seems like a repition of results.

VERSION 3 – AUTHOR RESPONSE

These statements are quoted from an article as indexed (ITA M Ponnighaus, Leprosy Review, 1990.61(4):366-74) with a slight hange. The author is professor in LSE. It is a fact that only a few (may 1 or 2) studies are there on incidence (cohort based) study and most are from cross section surveys.
However, I have slightly modified some of the sentences in abstract and introductions to make more meaningful.