CÂMARA DOS DEPUTADOS

REQUERIMENTO DE INFORMAÇÃO
Nº **3587**, de 2018

Do Sr. Deputado LUCIANO DUCCI

ao

MINISTÉRIO DA SAÚDE

CÂMARA DOS DEPUTADOS
Gabinete do Deputado **Luciano Ducci** – PSB/PR

REQUERIMENTO DE INFORMAÇÕES Nº 3587, DE 2018

(Do Sr. Luciano Ducci)

Solicita ao Ministro de Estado da Saúde informações a respeito da implantação do esquema único de 6 doses (MDT-U) para tratamento de pacientes de hanseníase no brasil.

Senhor Presidente:

Requeiro a V. Exa., com base no art. 50 da Constituição Federal, e nos arts. 115 e 116 do Regimento Interno que, ouvida a Mesa, sejam solicitadas informações ao Sr. Ministro de Estado da Saúde a respeito da a implantação do esquema único de 6 doses (Multidroga Terapia Esquema Único MDT-U) para tratamento de pacientes de hanseníase no brasil.

- Existe de fato a intenção do Ministério da Saúde em alterar o protocolo de tratamento para a hanseníase?
- Se positivo, qual é o modelo que poderá ser adotado para o referido tratamento?
- Quais são as evidências científicas para diminuir o tempo de tratamento dos antibióticos usados para o tratamento de hanseníase há quase 40 anos?
- As possíveis mudanças levarão em conta as manifestações dos Centros de Referência de Hanseníase, da Sociedade Brasileira de Hanseníase, bem como os outros profissionais da área?
- As referidas mudanças estão em consonância com os protocolos indicados pela Organização Mundial de Saúde?

Existem outros países no mundo que já utilizam o tratamento pretendido? Quais são os seus percentuais de eficácia em comparação com o atual protocolo adotado pelo Brasil?

Com relação ao ofício OF/PR/MG/C/1183/2018, datado do dia 09 de maio de 2018, remetido pela Procuradoria da República em Minas Gerais para a Secretaria de Vigilância em Saúde do Ministério da Saúde, quais foram os encaminhamentos adotados, sobretudo quanto à recomendação de suspenção de qualquer medida que pudesse alterar o atual protocolo de tratamento de hanseníase?

JUSTIFICAÇÃO

A neuropatia hansênica é a neuropatia periférica de etiologia infecciosa mais comum em todo o mundo, constituindo-se em um problema de saúde pública em muitos países. Além disso, trata-se de uma doença com elevado potencial incapacitante, com forte efeito de discriminação tanto social quanto funcional, sobretudo em decorrência das lesões e sequelas neurais deformantes e incapacitantes que provoca nos pacientes.

O Brasil registra cerca de 30 mil novos casos de hanseníase a cada ano, sendo responsável por mais de 90% dos casos das Américas. A altíssima incidência de casos com graves incapacidades neurais no momento do diagnóstico e a notificação de novos casos em crianças comprovam a demora no diagnóstico da doença, a persistência da transmissão ativa e o despreparo no reconhecimento das implicações dessa micobacteriose, evidenciando o controle epidemiológico ineficiente da hanseníase no país.

Em reunião no dia 18 de abril de 2018 no Ministério da Saúde (MS), o Comitê Técnico Assessor (CTA) de hanseníase foi informado que seria implantado no Brasil um esquema único de tratamento para pacientes de hanseníase, com os mesmos antibióticos usados há quase 40 anos, porém, com a

metade do tempo mínimo utilizado hoje para o tratamento dos pacientes multibacilares (MB), e com todos os antibióticos para todos, o que significa que mesmo pacientes paucibacilares (PB), hoje cerca de 30% no Brasil, teriam que usar rifampicina, dapsona e clofazimina, esta última usada atualmente somente nos pacientes MB.

Segundo informações as razões para esta conduta estão baseadas em um trabalho publicado na revista *PLOs Neglected Tropical Diseases*, que daria suporte à mudança do esquema.

A decisão do Ministério da Saúde preocupa os neurologistas com experiência na área, já que o reconhecimento do comprometimento neural, sobretudo na forma clínica neural primária ainda representa um grande desafio digno de consideração na prática clínica. O atraso no diagnóstico é quase certamente devido à falta de ferramentas diagnósticas disponíveis, corroborando para um subdiagnóstico. É importante destacar que quanto maior o tempo de evolução da doença (atraso diagnóstico), maior será a gravidade dos sintomas neurológicos e a quantidade de nervos comprometidos com acentuação das incapacidades. Tais dados são bem documentados em publicações científicas de reconhecimento internacional, desenvolvidas por investigadores na área com a notável contribuição de brasileiros que descrevem casos de hanseníase neural com evolução arrastada e comprometimento neural grave e incapacitante.

Uma das preocupações relativas à nova proposta terapêutica do Ministério da Saúde é a literatura que a fundamenta. Segundo informações, na referida literatura não foram incluídas investigações com base em métodos diagnósticos utilizados para o reconhecimento do comprometimento neural, tais como eletroneuromiografia (ENMG). A avaliação eletroneuromiográfica é de importância ímpar para o diagnóstico de neuropatia hansênica, pois possibilita o reconhecimento de lesão subclínica da disfunção neural.

A mudança de esquema terapêutico afetará definitivamente o tratamento e o futuro de milhares de pacientes. E diante disso a Sociedade Brasileira de Hanseníase se posicionou de maneira contrária à adoção do novo protocolo por parte do Ministério da Saúde, solicitando a suspenção das supracitadas medidas, visando promover um debate mínimo com usuários, e com as diversas entidades que representam profissionais de saúde e cientistas deste país, Brasil afora. Entretanto, tais apelos não foram atendidos e o Ministério da Saúde continua promovendo as tratativas para a implementação do novo protocolo de tratamento, que motivou a apresentação deste presente Requerimento de Informações, com o intuito de fazer com o que o Ministério da Saúde se posicione oficialmente sobre o tema em questão.

Logo, é imprescindível a obtenção das informações acima indicadas, por todos os motivos expostos, e também para que o Congresso Nacional possa exercer com amplitude a sua função de Fiscalização e Controle dos atos do Poder Executivo.

29 MAIO 2018

Sala das Sessões, em de de 2018.

Luciano Ducci
Deputado Federal
PSB/PR

CÂMARA DOS DEPUTADOS

30/05/2018
10:29

MESA DIRETORA DA CÂMARA DOS DEPUTADOS

DESIGNAÇÃO DE RELATOR

Designo relator da seguinte proposição o senhor Deputado Fábio Ramalho, Primeiro Vice-Presidente.

RIC 3.587/2018 - do Sr. Luciano Ducci - que "Solicita ao Ministro de Estado da Saúde informações a respeito da implantação do esquema único de 6 doses (MDT-U) para tratamento de pacientes de hanseníase no brasil. "

CÂMARA DOS DEPUTADOS
GABINETE DA PRIMEIRA-VICE-PRESIDÊNCIA

REQUERIMENTO DE INFORMAÇÃO Nº 3587/2018

Autor: Deputado Luciano Ducci - PSB/PR

Destinatário: Ministro de Estado da Saúde

Assunto: Solicita ao Ministro de Estado da Saúde informações a respeito da implantação do esquema único de 6 doses (MDT-U) para tratamento de pacientes de hanseníase no brasil.

Despacho: O presente requerimento de informação está de acordo com a Constituição Federal, artigo 50, § 2º, e com o Regimento Interno da Câmara dos Deputados, artigos 115 e 116. Dispensado o relatório em conformidade com o § 1º do artigo 2º do Ato da Mesa nº 11/1991, o parecer é pelo **encaminhamento**.

Primeira-Vice-Presidência, em 14 de junho de 2018

Fábio Ramalho
Primeiro-Vice-Presidente

Câmara dos Deputados

RIC 3.587/2018

Autor: Luciano Ducci

Data da Apresentação: 29/05/2018

Ementa: Solicita ao Ministro de Estado da Saúde informações a respeito da implantação do esquema único de 6 doses (MDT-U) para tratamento de pacientes de hanseníase no brasil.

Forma de Apreciação: .

Texto Despacho: Aprovação pelo Presidente, Dep. Rodrigo Maia, "ad referendum" da Mesa, do parecer do senhor Deputado Fábio Ramalho, Primeiro Vice-Presidente, pelo encaminhamento.

Regime de tramitação: .

Em 20/06/2018

RODRIGO MAIA
Presidente da Câmara dos Deputados

Ofício 1ªSec/RI/E/nº 2297/18 Brasília, 25 de junho de 2018.

A Sua Excelência o Senhor
GILBERTO OCCHI
Ministro de Estado da Saúde

Assunto: **Requerimento de Informação**

RECEBI NESTA DATA A PRESENTE DOCUMENTAÇÃO.
EM 25/06/18
Nome por extenso e legível: Mateus José
Ponto:

Senhor Ministro,

Nos termos do art. 50, § 2º, da Constituição Federal, encaminho a Vossa Excelência cópia(s) do(s) seguinte(s) Requerimento(s) de Informação:

PROPOSIÇÃO	AUTOR
Requerimento de Informação nº 3574/2018	Alan Rick
Requerimento de Informação nº 3578/2018	Renzo Braz
Requerimento de Informação nº 3587/2018	Luciano Ducci
Requerimento de Informação nº 3592/2018	Odorico Monteiro
Requerimento de Informação nº 3595/2018	Lucas Vergilio

Por oportuno, solicito, na eventualidade de a informação requerida ser de natureza sigilosa, seja enviada também cópia da decisão de classificação proferida pela autoridade competente, ou termo equivalente, contendo todos os elementos elencados no art. 28 da Lei nº 12.527/2011 (Lei de Acesso à Informação), ou, caso se trate de outras hipóteses legais de sigilo, seja mencionado expressamente o dispositivo legal que fundamenta o sigilo. Em qualquer caso, solicito ainda que os documentos sigilosos estejam acondicionados em invólucro lacrado e rubricado, com indicação ostensiva do grau ou espécie de sigilo.

Atenciosamente,

Deputado GIACOBO
Primeiro-Secretário

- NOTA: os Requerimentos de Informação, quando de autorias diferentes, devem ser respondidos separadamente.
/LMR

MINISTÉRIO DA SAÚDE

Aviso nº 347/2018-ASPAR/GM/MS

Brasília, 25 de junho de 2018.

A Sua Excelência o Senhor
Deputado GIACOBO
Primeiro-Secretário da
Câmara dos Deputados

Assunto: Requerimento de Informação.

Senhor Primeiro-Secretário,

Reportando-me ao Ofício 1ª Sec/RI/E/nº 2297/2018, referente ao Requerimento de Informação nº 3587/2018, do Deputado LUCIANO DUCCI, em que foram solicitadas deste Ministério informações referentes a implantação do esquema único de 6 doses (MDT-U) para tratamento de pacientes de hanseníase no Brasil, encaminho resposta com os esclarecimentos prestados pela Secretaria de Vigilância em Saúde.

Atenciosamente,

GILBERTO OCCHI
Ministro de Estado da Saúde

Documento assinado eletronicamente por **Gilberto Magalhães Occhi, Ministro de Estado da Saúde**, em 28/06/2018, às 17:45, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015; e art. 8º, da Portaria nº 900 de 31 de Março de 2017.

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Referência: Processo nº 25000.110393/2018-27 SEI nº 4461931

PRIMEIRA-SECRETARIA
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Em 29 / 06 / 18 às 11 h 02
Servidor
2396
Ponto
Portador

MINISTÉRIO DA SAÚDE

DESPACHO

SVS/MS

Brasília, 12 de junho de 2018.

À: Assessoria Parlamentar - ASPAR

Assunto: **Solicita informações a respeito da implantação do esquema único de 6 doses (MDT-U) para tratamento de pacientes de Hanseníase no Brasil.**

Restituo a essa Assessoria Parlamentar, o Processo (25000.094587/2018-78), referente ao assunto supracitado, de interesse do Senhor Deputado Luciano Ducci, após manifestação do Departamento de Vigilância das Doenças Transmissíveis - DEVIT, por meio da Nota Informativa (4121820), para conhecimento e providências no que couber.

Atenciosamente,

Osnei Okumoto
Secretário de Vigilância em Saúde

Documento assinado eletronicamente por **Osnei Okumoto, Secretário(a) de Vigilância em Saúde**, em 12/06/2018, às 15:46, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015; e art. 8º, da Portaria nº 900 de 31 de Março de 2017.

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MINISTÉRIO DA SAÚDE

DESPACHO

DEVIT/SVS/MS

Brasília, 08 de junho de 2018.

A: DIAD/SVS

Referência: Requerimento 3587/2018

Assunto: Encaminha Nota Informativa Nº 15/2018-CGHDE/DEVIT/SVS/MS

Encaminho Nota Informativa Nº 15/2018-CGHDE/DEVIT/SVS/MS (4121820) de interesse do Excelentíssimo Senhor Deputado Dr. Luciano Ducci, que solicita informações a respeito da implantação do esquema único de 6 doses (MDT-U) para tratamento de pacientes de Hanseníase no Brasil.

Departamento de Vigilância das Doenças Transmissíveis

Documento assinado eletronicamente por **André Luiz de Abreu, Diretor(a) do Departamento de Vigilância das Doenças Transmissíveis**, em 12/06/2018, às 10:28, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015; e art. 8º, da Portaria nº 900 de 31 de Março de 2017.

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MINISTÉRIO DA SAÚDE
COORDENAÇÃO-GERAL DE HANSENÍASE E DOENÇAS EM ELIMINAÇÃO - CGHDE
SRTV 702, Via W5 Norte - Bairro Asa Norte, Brasília/DF, CEP 70723-040
Site - saude.gov.br

NOTA INFORMATIVA Nº 15/2018-CGHDE/DEVIT/SVS/MS

Informa sobre a implantação do esquema único de tratamento da Hanseníase.

1. Atendendo ao requerimento RIC 3587/2018, do senhor Deputado Luciano Ducci, a respeito do esquema único de tratamento para a Hanseníase, denominado Multidrogaterapia (MDT-U) no Brasil, o Ministério da Saúde esclarece abaixo os questionamentos.

2. O Ministério da Saúde está analisando o novo protocolo para o tratamento da Hanseníase no Brasil, realizando desde dezembro de 2017, discussões sobre esse tema no Comitê Técnico Assessor de Hanseníase (CTA) , composto por representantes das Sociedades Brasileiras de Hansenologia, de Dermatologia, de Enfermagem e de Fisioterapia, Departamento de Atenção Básica (DAB/SAS/MS), Conselho Nacional dos Secretários Estaduais (CONASS) e Conselho Nacional das Secretarias Municipais de Saúde (CONASEMS), Movimento de Reintegração das Pessoas Atingidas pela Hanseníase (Morhan) e especialistas de Referências Nacionais, entre outros.

3. A proposta é a de tratamento único em Unidades Básicas de Saúde e em serviços especializados para pessoas diagnosticadas com hanseníase com seis doses de Polioquimioterapia Multibacilar (PQT), independente da classificação operacional Paucibacilar (PB) ou Multibacilar (MB). Atualmente, tal tratamento é realizado em seis doses para pacientes classificados como PB e doze meses para pacientes MB.

4. Até o momento foram publicados 17 artigos científicos de pesquisas desenvolvidas com o tema MDT-U em periódicos como International Journal of Dermatology, Leprosy Review e PLOS Neglected Tropical Diseases. As pesquisas foram realizadas na Índia, China, Bangladesh e Brasil e produziram evidências que indicam a eficácia do MDT-U para o tratamento da hanseníase. Em anexo, estão os principais artigos.

5. O Ministério da Saúde, a partir do diálogo aberto no CTA com os principais envolvidos no tema da Hanseníase no Brasil, vem realizando discussões e considera as observações feitas pelos especialistas e movimentos sociais em agendas abertas para essa finalidade, realizando oficinas macrorregionais com profissionais e especialistas, inclusive, Videoconferências com os estados.

6. O Brasil, em sua política pública de saúde, segue as orientações da Estratégia Global para a Hanseníase da Organização Mundial de Saúde (OMS) e contribui, por meio de suas ações, para um mundo sem hanseníase.

7. Considerando o amparo científico dos estudos supracitados, realizados por tempo considerável, e diante da realidade epidemiológica vigente de país com alta carga da hanseníase, caso seja implantado o MDT-U, o Brasil será o primeiro país do mundo a adotar esse esquema de tratamento, tal como foi um dos primeiros países do mundo a adotar a Poliquimioterapia (PQT) na década de 80, frente à resistência de outros países.

8. A implantação do novo protocolo encontra respaldo nos estudos mencionados, nas evidências e nos resultados produzidos ao longo de pesquisas, que contabilizam de um modo geral quinze anos. Outra razão que justifica o novo protocolo é o enfrentamento de um problema identificado ao longo do acompanhamento dos pacientes, que apresentam preocupantes taxas de abandono ao tratamento em decorrência do tempo e das reações adversas pelo uso prolongado que a PQT exige. Frente ao exposto e almejando a melhoria da qualidade de vida desses pacientes, sua recuperação e cura com a redução da carga da doença, o Ministério da Saúde tem reforçado as discussões para a possível implantação do MDT-U.

9. É importante ressaltar que, conforme recomendado no OF/PR/MG/C/11832018, de 09 de maio de 2018, o Ministério da Saúde não adotou qualquer medida que pudesse alterar o atual protocolo de tratamento de hanseníase. O embasamento para tomada de qualquer decisão aguarda parecer técnico da Comissão Nacional de Incorporação de Tecnologias no SUS (Conitec).

10. Esta Secretaria de Vigilância em Saúde está à disposição para informações complementares.

CARMELITA RIBEIRO FILHA

Coordenadora-Geral de Hanseníase e Doenças em Eliminação

Documento assinado eletronicamente por **Carmelita Ribeiro Filha**, **Coordenador(a)- Geral de Hanseníase e Doenças em Eliminação**, em 08/06/2018, às 09:56, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015; e art. 8º, da Portaria nº 900 de 31 de Março de 2017.

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Brasília, 04 de junho de 2018.

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Uniform multidrug therapy for leprosy patients in Brazil (U-MDT/CT-BR): Results of an open label, randomized and controlled clinical trial, among multibacillary patients

Gerson Oliveira Penna[1]*, Samira Bührer-Sékula[2]*, Lígia Regina Sansigolo Kerr[3], Mariane Martins de Araújo Stefani[2], Laura Cunha Rodrigues[4], Marcelo Grossi de Araújo[5], Andrea Machado Coelho Ramos[5], Ana Regina Coelho de Andrade[5], Maurício Barcelos Costa[6], Patricia Sammarco Rosa[7], Heitor de Sá Gonçalves[8], Rossilene Cruz[9], Maurício Lima Barreto[10], Maria Araci de Andrade Pontes[8], Maria Lúcia Fernandes Penna[11]

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OPEN ACCESS

Citation: Penna GO, Bührer-Sékula S, Kerr LRS, Stefani MMdA, Rodrigues LC, de Araújo MG, et al. (2017) Uniform multidrug therapy for leprosy patients in Brazil (U-MDT/CT-BR): Results of an open label, randomized and controlled clinical trial, among multibacillary patients. PLoS Negl Trop Dis 11(7): e0005725. https://doi.org/10.1371/journal.pntd.0005725

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

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Abstract

Background

Leprosy control is based on early diagnosis and multidrug therapy. For treatment purposes, leprosy patients can be classified as paucibacillary (PB) or multibacillary (MB), according to the number of skin lesions. Studies regarding a uniform treatment regimen (U-MDT) for all leprosy patients have been encouraged by the WHO, rendering disease classification unnecessary.

Methodology and findings

An independent, randomized, controlled clinical trial conducted from 2007 to 2015 in Brazil, compared main outcomes (frequency of reactions, bacilloscopic index trend, disability progression and relapse rates) among MB patients treated with a uniform regimen/U-MDT (dapsone+rifampicin+clofazimine for six months) *versus* WHO regular-MDT/R-MDT (dapsone+rifampicin+clofazimine for 12 months). A total of 613 newly diagnosed, untreated MB patients with high bacterial load were included. There was no statistically significant difference in Kaplan-Meyer survival function regarding reaction or disability progression among patients in the U-MDT and R-MDT groups, with more than 25% disability progression in both groups. The full mixed effects model adjusted for the bacilloscopic index average trend in

www.cnpq.br/). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors themselves received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

time showed no statistically significant difference for the regression coefficient in both groups and for interaction variables that included treatment group.

During active follow up, four patients in U-MDT group relapsed representing a relapse rate of 2.6 per 1000 patients per year of active follow up (95% CI [0·81, 6·2] per 1000). During passive follow up three patients relapsed in U-MDT and one in R-MTD. As this period corresponds to passive follow up, sensitivity analysis estimated the relapse rate for the entire follow up period between 2·9- and 4·5 per 1000 people per year.

Conclusion

Our results on the first randomized and controlled study on U-MDT together with the results from three previous studies performed in China, India and Bangladesh, support the hypothesis that UMDT is an acceptable option to be adopted in endemic countries to treat leprosy patients in the field worldwide.

Trial registration

ClinicalTrials.gov: NCT00669643

Author summary

Since the introduction of multidrug therapy for leprosy in the 80's, different classification criteria for leprosy patients have been proposed and treatment has been progressively shortened. Currently, leprosy patients are classified into paucibacillary/PB and multibacillary/MB based on the number of skins lesions. MB patients (over 5 skin lesions) receive three drugs (rifampicin, dapsone, clofazimine) for 12 months, while PB patients (up to 5 skin lesions) receive two drugs (rifampicin, dapsone) for 6 months. We conducted a randomized clinical trial to evaluate the efficacy of a uniform treatment (U-MDT) for both PB and MB leprosy patients, regardless any classification criteria. The current study includes results from: laboratory tests (bacilloscopic index/BI, serology and histopathology), clinical evaluation during a long follow-up, and uses adequate epidemiological analysis that gives robust evidence on main parameters used to evaluate the efficacy of U-MDT.

This study reports data among MB leprosy patients treated with regular/R-MDT and uniform/U-MDT regarding: (i) The frequency of leprosy reactions; (ii) BI decrease, (iii) Disability progression and (iv) Relapse. Overall, our results showed that there was no statistically significant difference in these outcomes for both treatment groups. In this sense, U-MDT can be considered as part of leprosy policy by control programs in endemic countries.

Introduction

In 1981, the World Health Organization (WHO) recommended the use of multidrug therapy (MDT) for leprosy. Since then, the disease prevalence dropped, but the case detection rate did not decrease and currently many countries still present high detection rates [1]. According to the WHO, in 2014 more than 200.000 new leprosy cases were detected worldwide. Additionally, since the implementation of MDT in early 80's, the duration of treatment has been halved

from 24 to 12 months for MB patients and from 12 to 6 months for PB patients. On the other hand, no new standard treatment scheme for leprosy patients has been proposed. Leprosy remains a poorly understood infectious disease and in several endemic countries its diagnosis, treatment and control have been carried out in large scale, yet the effectiveness of these programs is yet uncertain [2].

Leprosy is caused by *Mycobacterium leprae*, a highly infectious microorganism with low virulence, meaning that only a small proportion of those infected will manifest the disease. Leprosy presents a wide spectrum of clinical manifestations, reflecting the interaction of the bacilli and the immune response of the host. In 1966, Ridley and Jopling proposed a disease classification system based on clinical, histological and bacteriological data. This classification includes two polar forms, tuberculoid (TT) and lepromatous (LL) in which TT patients present with few bacilli and strong cellular immunity response while LL ones have high bacterial load and weak cellular immunity. Additionally, three intermediary forms lie between the poles: borderline-tuberculoid (BT), borderline (BB), and borderline lepromatous (BL) [3]. Later, an early indeterminate leprosy form (I) was included in this classification system. In 1982, the WHO recommended two standardized multidrug therapy (MDT) regimens for leprosy, one for I, TT and BT leprosy cases and the other for BB, BL and LL cases. However since this classification requires clinical, histological and bacteriological data, it was very difficult for leprosy control fieldworkers to adopt it. Therefore, the classification system for treatment purposes has been later simplified to two leprosy types: paucibacillary leprosy (PB) referring to patients with a low bacillary load, and multibacillary (MB) patients with high bacillary load, based on results from bacilloscopy of Ziehl–Neelsen stained skin smears. The WHO classification into MB or PB patients for treatment purposes proposed in 1997 is based on the number of skin lesions as a proxy for the bacteriological data and defines two different treatment regimens: MB patients (over 5 skin lesions) receive twelve months of daily dapsone plus clofazimine and monthly rifampicin doses while for PB patients (up to 5 skin lesions), treatment consists of six months of daily dapsone plus monthly rifampicin doses. The rationale for these two regimens is that the probability of the presence of a naturally resistant bacillus, among those infecting a patient, is proportional to the bacillary load. Also, in order to avoid the selection of drug resistant bacilli, patients with high bacillary load need to be treated longer and with one additional drug [4]. On the other hand, to avoid side effects, patients with low bacillary load should not be over treated.

The duration of treatment for leprosy and tuberculosis has always been a controversial issue due to the presence of persistent bacilli. In leprosy, the permanence of bacilli, despite months or years of chemotherapy is probably due to the fact that *M. leprae* has low multiplication rate, *i.e.*, low metabolism, making this pathogen less susceptible to destruction by chemotherapy.

Leprosy control programs are based on early diagnosis and treatment of cases, *i.e.*, elimination of infectious sources and the relapse rate is considered the main treatment outcome. In this context, the operational WHO classification system based on the number of skin lesions can lead to misclassifications of MB as PB cases, consequently increasing the chances of relapses. During the chronic course of leprosy, new neurological damage leading to further physical disability can occur. In the perspective of the patient and also of the medical care staff, disability is an important clinical outcome that has never been included in leprosy chemotherapy trials [5].

The uniform treatment for leprosy (U-MDT) consists of daily intake of dapsone plus clofazimine and monthly rifampicin for six months, despite any type of patient's classification. Therefore, the adoption of a uniform treatment for all cases would render disease classification unnecessary, simplifying the implementation of leprosy treatment at primary care. The need

for evaluating a uniform treatment for leprosy patients was included in the WHO Technical Advisory Group report in 2002, and in 2003 a WHO U-MDT trial without a control group was launched in India and China [6].

This original report describes for the first time, long-term results of the four main outcomes of MB patients that participated in the open label randomized Clinical Trial of Uniform Multidrug Therapy conducted in Brazil (U-MDT/CT-BR), concerning: (i) frequency of reactions; (ii) trends of bacteriological index (BI) during treatment and follow up; (iii) disability progression; and (iv) relapse rates [7] and [8].

Methods

Ethics considerations

This study was performed under the international (Helsinki) and Brazilian research regulations and was approved by the National Ethics Commission of Research (CONEP) of the Ministry of Health, protocol number 12949/2007. Written informed consent was required from all the patients prior to their inclusion in the study. For patients aged six to 17 years, written parental consent was mandatory. Data confidentiality was strictly guaranteed. Patients were free to leave the study, if they desired, and opt for the R-MDT regimen outside the study.

Study design

An open label randomized clinical trial was conducted, from March 2007 to January of 2015, at two Brazilian leprosy reference centres (Fundação Alfredo da Matta (FUAM) in Manaus, Amazonas State, north region and Centro de Dermatologia Dona Libânia (CDERM) in Fortaleza, Ceará State, northeast region). ClinicalTrials.gov registered its protocol under the identifier–NCT 00669643. In this trial, all patients coming to these dermatology clinics, which are in charge of treating skin diseases in general, were examined. In this report, the study population included newly diagnosed, previously untreated PB and MB leprosy patients and returning defaulters and relapse cases, provided that the last treatment dose was taken more than five years prior to the enrollment in the study. All of the leprosy patients were between six- 65 years old. Patients were excluded if they were receiving tuberculosis/TB or steroid treatment, had overt signs of acquired immune deficiency syndrome, they did not reside permanently in the area or were unable to visit the clinic every month during the treatment and follow-up periods. Patients were classified as MB according to the criteria proposed by the WHO, *i.e.*, patients with more than five skin lesions. Until 2011, the study included 613 newly diagnosed MB leprosy patients with high bacterial load and among them, 323 were randomized into the U-MDT group and 290 into the WHO regular regimen (R-MDT) group.

Sample size

In order to ensure a precise estimate of relapses among MB patients, a sample size of at least 278 MB patients in each study arm was calculated. This value is based on an *alfa* error of 0·05 a *betta* error of 0·20, i.e., a power of 80%, a ten years relapse risk for the U-MDT group of nine per cent, and a relapse risk of 0·03 in the R-MDT group for the same period.

Randomization

Before starting the randomization and the controlled clinical trial, all study protocols (standard operational procedures/SOP) and clinical report forms (CRF) were evaluated in an open and uncontrolled cohort pilot study with 78 patients, conducted from 2004–2006 at the Federal University of Minas Gerais, Brazil.

Randomization was performed in order to evaluate whether there were differences in the two treatment modalities. All patients who met the inclusion criteria, independent of MB or PB status were randomized into the experimental (U-MDT) or the control (R-MDT) group. Prompt action was essential because the experimental treatment group for PB patients began treatment with three drugs while the control group was treated with two drugs. Since for MB patients the drug regimen was the same for U-MDT and R-MDT, differing only in its duration, MB patients were randomized after six months of initiating therapy when the U-MDT group discontinued treatment, while the control R-MDT group continued treatment for additional six months.

Procedures

A randomization table was created with codes for all patients in the study, based on a random list of numbers, using the study entrance sequence according to the CRF number. For this process, the space in the worksheet that contained the randomization code was covered with the same material used in lottery scratch cards, so that the printed numbers were not visible. This code determined the directions for treatment group of each patient as follows: when the code corresponded to an odd number, the patient was part of the experimental group 1 or 3 (U-MDT), according to their classification as PB or MB, respectively. When the code corresponded to an even number, the patient was part of control group 2 or 4 (R-MDT), according to the classification as PB or MB, respectively. A spreadsheet containing the codes was sent to the local coordinator of each recruiting centre, which was responsible for the allocation of the patients into the study groups. For PB patients, the randomization results were identified immediately after the inclusion of the patient into the study.

The randomization code of each MB case was kept blind in the spreadsheet until the patient completed six doses of the MDT regimen, when the local coordinator disclosed the code. During this trial, the local research coordinators were responsible for managing data collection according to the eligibility criteria and for ensuring the six doses of MDT, keeping the patient randomization spread sheet under his/her responsibility and coordinating treatment for each patient. In each centre, the data manager was responsible for coordinating the preparation of the spreadsheet with the randomization codes and for maintaining a confidential copy of the spreadsheet containing the randomization results.

At the first visit, the dermatologist in charge performed a complete clinical examination that included registering the number of skin lesions and affected nerves and collecting skin biopsies for histopathological examination. Health workers collected blood for liver and renal function tests, complete blood count, anti-PGL-I ML Flow test and skin smear material from six sites, including ear lobes and elbows, for bacilloscopy. In each centre, a technician with extensive experience, examined the Ziehl-Nielsen stained skin smears and generated a bacilloscopic index (BI) that ranged from zero to six crosses for each skin site and results were summarized as the average of all six BI (aBI).

During the first year of follow up, patients had a monthly appointment and thereafter, yearly. The visits included dermato-neurologic examination, blood collection to evaluate liver function and whole blood counts. Skin smears were collected at the beginning and at the end of treatment and thereafter yearly. Physicians advised all patients to come to an urgent appointment in case any sign or symptom of leprosy reaction occurred. Treatment for reaction was established by the assistant dermatologist and registered in the CRF, and followed the guidelines established by the Brazilian leprosy control program from the Ministry of Health.

Recurrent leprosy was defined as the reappearance of signs and symptoms of the disease after completion of MDT, not associated with leprosy reactions, and with an increase in the

bacillary index (BI) compared to the BI after treatment completion. Patients with suspicion of relapse were clinically reviewed by the research PI (GOP), by the assistant dermatologist and by Dr. Sinesio Talhari, an expert member of the independent steering committee, when skin smears and biopsies were collected.

Disability grade of each patient was the highest grade reported in either eye, foot and hand as recommended by the WHO. Neurological examination indicating disability in one of these sites that was previously unaffected was considered as disability progression (DP) and was used to compare neurological damage in the two study groups. The protocol, the study design, preliminary results of this trial, and the patients' profile and satisfactions have been published [7,9,10].

Statistical analyses

We used Student *t* test for continuous variables and *Chi-square* for dichotomous ones to compare the distribution of the baseline characteristics in each study arm. We evaluated the first reaction since the beginning of treatment using a Kaplan-Meyer survival function for the experimental and the control groups and a log-rank test. The survival analysis included the first six months of treatment. To compare the number of reaction episodes between the two groups after 180 days of treatment, we fitted a Zero-inflated negative binomial regression model to the number of reaction as the dependent variable and the treatment group as the independent variable with the log of follow up days of each patient as an offset variable.

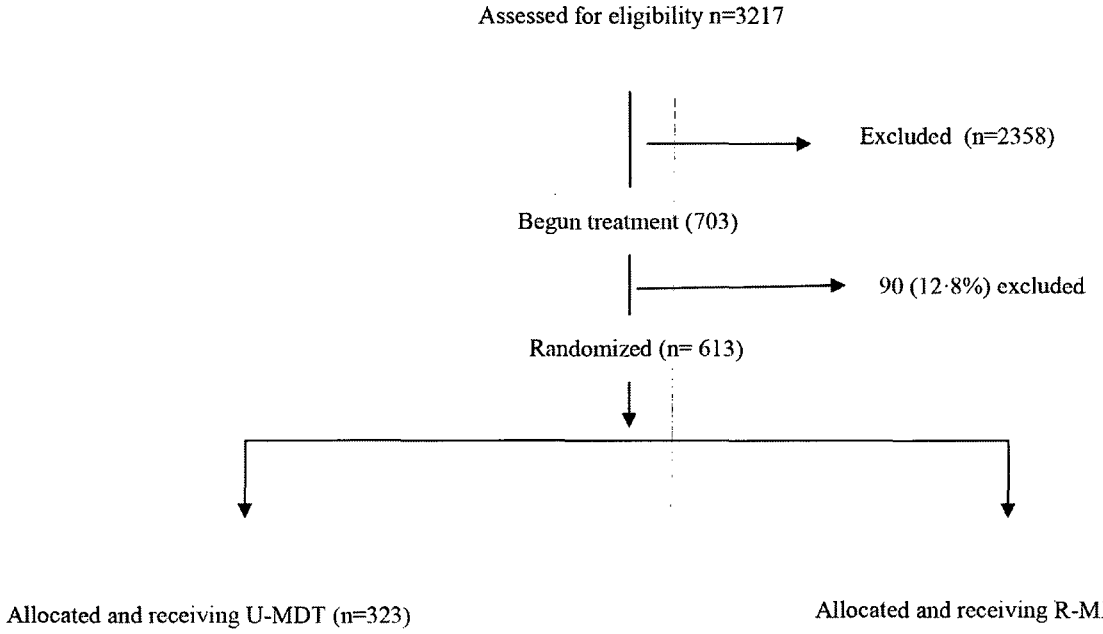
In order to evaluate the BI trend over time after 180 days from the onset of treatment, we fixed a multilevel linear model with mixed effects, i.e., a random intercept model. The aBI (average BI) was the independent variable and the dependent variables were time (in days), initial aBI categorized as high ($aBI \geq 4$) and low ($aBI < 4$), study arm (U-MDT and control), and three interaction variables combining the previous ones, two by two. For this analysis, time zero was the first day of the seventh month after the beginning of treatment, i.e., the randomization moment for MB patients. For clarity, the categorized aBI is referred as BI level, in contrast with aBI referring to continuous measure, the average of all sites of smear collection. We evaluated the first disability progression since the beginning of treatment using a Kaplan-Meyer survival function for experimental and control groups and a log-rank test. These survival analyses included the first six months of treatment. We estimated the difference of survival proportion in fixed points of time according to Kaplan Meyer curve and its confidence interval.

Results

Among the 3217 new cases registered for leprosy treatment at the two reference centers during the specified 4-year period, 859 (156 PB and 703 MB) agreed to participate in the trial. After deducting 90 (12.8%) MB patients for irregularity, 613 MB subjects were randomized to the treatment groups (323 to U-MDT and 290 to R-MDT). From these, 439 (71,7%) complied to the five years follow up period (239 in U-MDT and 200 in R-MDT). Fig 1 shows the participants' flow diagram.

In our study population, the total person-time of follow up was 3833·91 person-years, 1568·11 in the U-MDT group and 2265·8 in the R-MDT group. The median follow up time was 4·87 years for both groups, 4·86 years for U-MDT treatment group and 4·77 for R-MDT, meaning that half of the participants were followed for more than 4 years and 10 months.

The baseline characteristics of the two groups (Table 1) show a small unbalance between the intervention and the control group in relation to the aBI, but the two groups are comparable in all other variables.



Loss of follow-up

FOLLOW UP YEARS	*N*
LESS THAN 1 YEAR	*16**
1 TO <2	*30*
2 TO <3	*18*
3 TO <4	*12*
4 TO <5	*14*
TOTAL	*84*

* other diseases 8

Loss of follow-up

Followup years	
Less than 1 year	16*
1 to <2	23
2 to <3	11
3 to <4	17
4 to <5	17
total	90

* Death 1, other diseases 6

Fig 1. MB Patients' selection flow diagram.

https://doi.org/10.1371/journal.pntd.0005725.g001

(i) Frequency of leprosy reactions among MB patients

Figs 2 and 3 show the *Kaplan-Meyer* function of the survival without reaction in both treatment arms and also stratified by BI level. The *logrank test* for the survival curves showed no statistically significant difference between groups. By the 180th day (six months) of treatment, 64.14% of participants in U-MDT and 62.23% in R-MDT group were reaction-free indicating a risk ratio for at least one reaction at the period of 1·05, $CI_{95\%}$ [0·8554–1·2968]. Regarding the number of leprosy reactions developed in each treatment group, the negative binomial model fitted to the data showed no statistically significant difference compared with the intercept only model (log likelihood ratio (LLR) test = 2·9730, df = 2, p = 0·7681). These results indicate

Table 1. Main baseline characteristics of multibacillary leprosy patients stratified according to U-MDT and R-MDT Groups.

CHARACTERISTIC	U-MDT (n = 323)		R-MDT (n = 290)	
MEAN AGE (years) [a]	39.63		40.76	
AGE GROUPS (years) [b]				
0–9	5	1.55%	6	2.07%
10–19	24	7.43%	26	8.97%
40–49	68	21.05%	68	23.45%
30–39	59	18.27%	51	17.59%
20–29	61	18.89%	51	17.59%
50–59	72	22.29%	65	2241%
= > 60	34	10.53%	23	7·93%
GENDER [b]				
MALE	217	67.18%	193	66.55%
FEMALE	106	32.82%	97	33.45%
BI[b] (mean)	2·49		2·46	
BI GROUP				
BI<4	169	52·32%	145	50·00%
BI> = 4	154	47.68%	145	50.00%
Ridley Jopling Classification[b]				
I	3	0.93%	2	0.69%
LL	71	21.98%	59	20.42%
BT	93	28.79%	77	26.64%
BB	71	21.98%	71	24.22%
BL	85	26.32%	81	28.03%

U-MDT: uniform 6 months MDT regimen; R-DMT: regular 12 months MDT; BI: bacilloscopic index; I: indeterminate leprosy; LL: lepromatous leprosy; BT: borderline tuberculoid leprosy; BB: borderline borderline leprosy; BL: borderline lepromatous leprosy

[a] t test, p >0·05

[b] χ^2 test, p>0·05.

https://doi.org/10.1371/journal.pntd.0005725.t001

lack of association between the number of reactions and the treatment group (p value for the coefficient = 0,221), meaning that the treatment group did not affect the number of reactions. When patients were stratified into the aBI as $\geq$ or $<$ 4, no statistically significant difference in the development of leprosy reactions was seen between the study U-MDT and control R-MDT groups.

(ii) BI decrease

Fig 4 shows the aBI as a function of time for each MB patient, and Fig 5 shows the linear adjusted aBI as a function of time. These two figures illustrate the need for a multilevel model for analysis, as a patient aBI at a fixed time is dependent on the previous aBI measure. This analysis approach considers the BI time trend of each patient instead of the BI average of all patients in each time point representing treatment duration.

The full mixed effects model adjusted for the aBI trend—independent variables: treatment group, aBI level and time, plus three interaction variables—*initial aBI and group; time and group; initial aBI and time*—showed no statistical significance for the regression coefficient of bacilloscopic index of treatment groups and for interaction variables that included treatment group ('*group X time*' and '*group X initial aBI*'). The full model allowed for treatment effect on

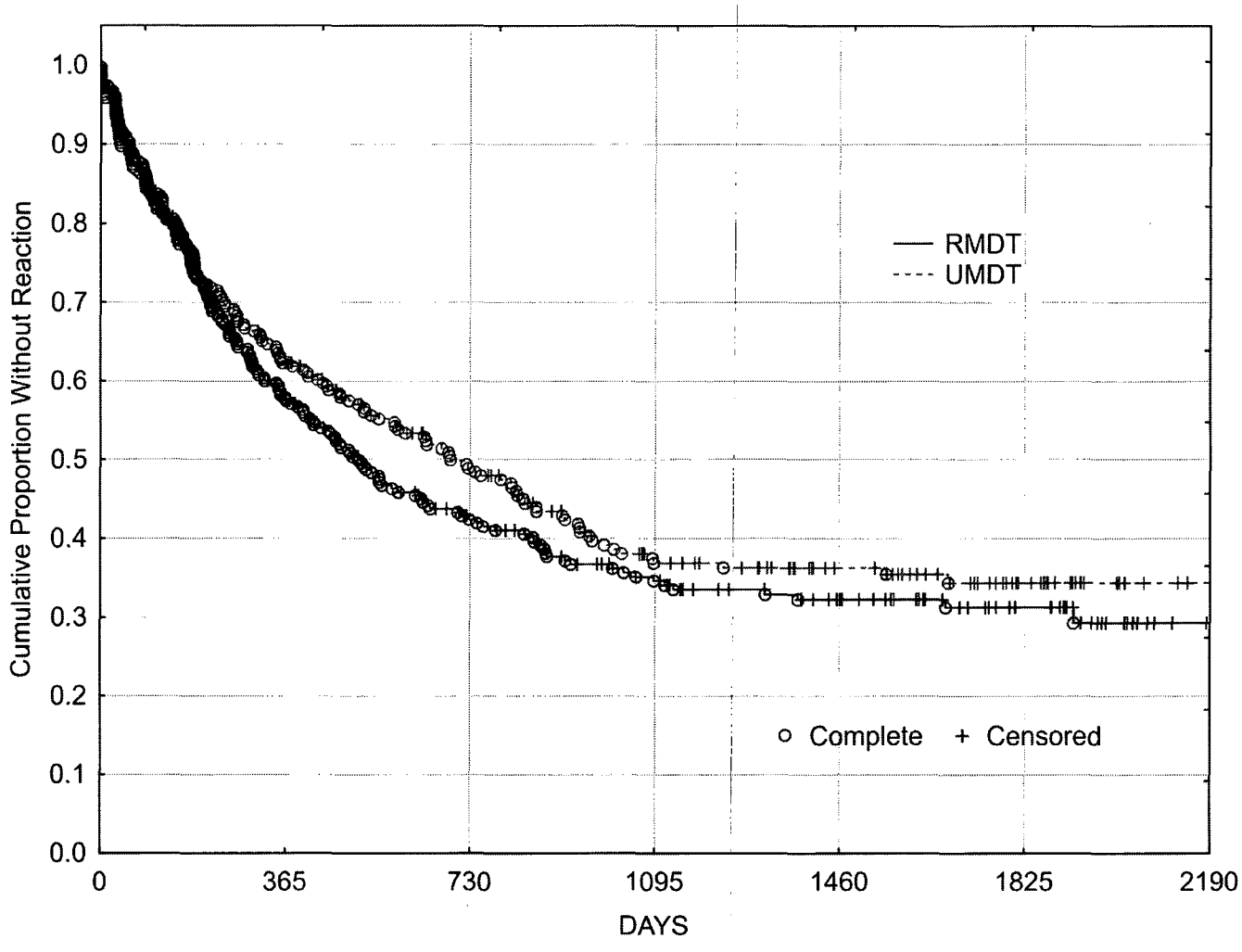


Fig 2. Kaplan Meyer survival curve of reaction free multibacillary leprosy patients comparing U-MDT *versus* R-MDT groups.

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aBI value, on time trend of aBI value and on different effect according to initial aBI. The final model retained the possible effect of treatment (group variable) on aBI value, of initial aBI effect on aBI value and of initial aBI effect (interaction of initial aBI and time variable) on time trend of aBI.

Table 2 shows the final model excluding these two not statistically significant interaction variables. The log likelihood ratio test comparing the two models showed no statistically significant difference in BI decrease. Fig 6 shows the daily BI decrease in MB patients in U-MDT and R-MDT after 180 days of starting treatment and the BI level, with its 95% confidence interval. No statistically significant difference was observed in the BI decrease of MB leprosy patients from the U-MDT and R-MDT groups.

(iii) Disability progression

Figs 7 and 8 show the cumulative probability survival without disability progression as a function of time of follow up. The *logrank* test for the survival curves showed no statistically significant difference between the two treatment groups. At the fifth year after the beginning of the

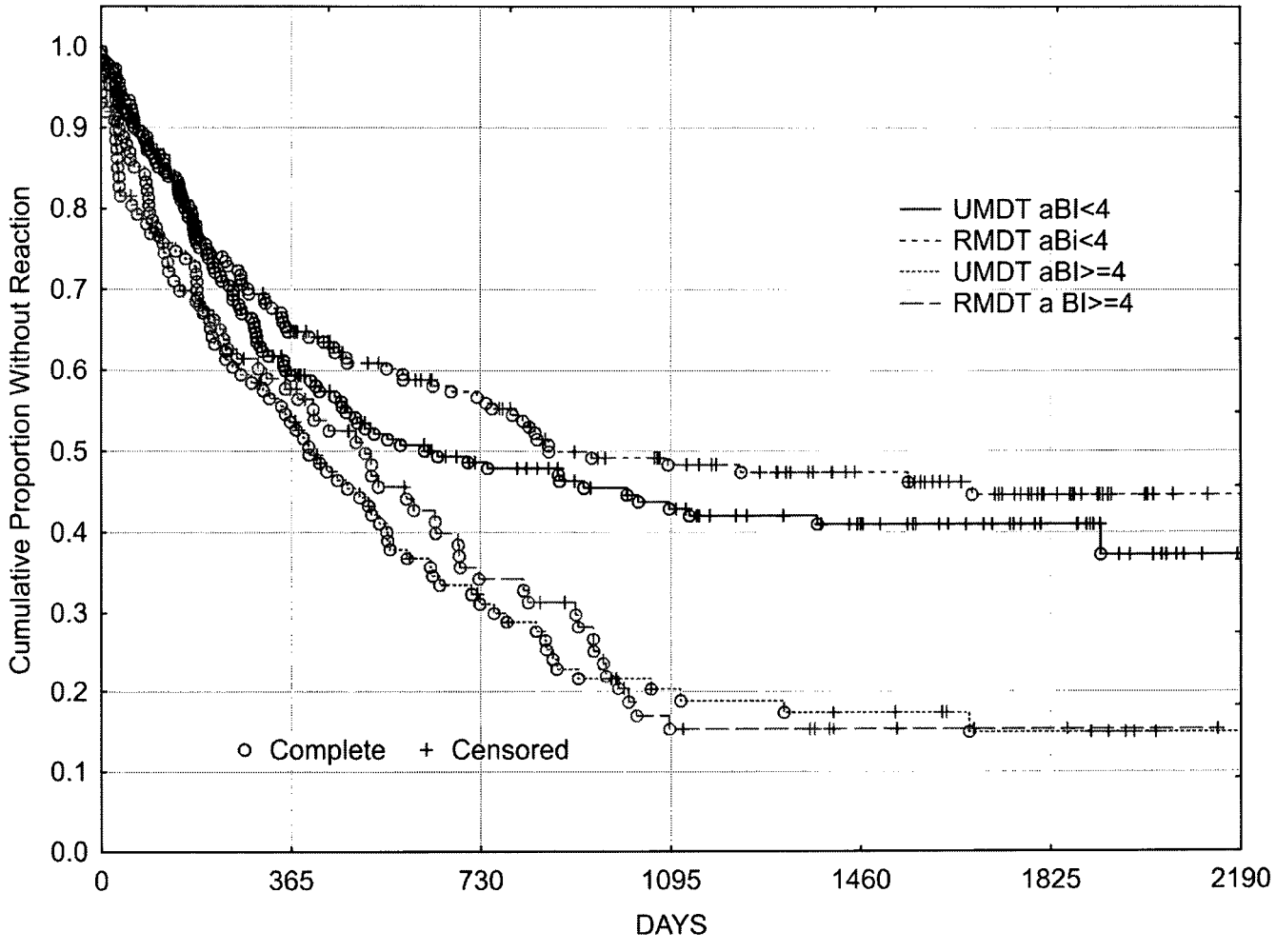

Fig 3. Kaplan Meyer survival curve of reaction free multibacillary leprosy patients: Comparing U-MDT *versus* R-MDT groups by the average bacilloscopic index/ aBI level.

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treatment (1825 days), 33.8% of U-MDT patients had disability progression compared with 30.06% of patients in the R-MDT group, 3.74% difference, 95% CI [- 3.2%, 12.08%]. For those with aBI < 4, the difference was 2.85% and 95% CI [-6.11%, 11.81%] and for those with aBI ≥ 4 the difference was 4.68% and 95% CI [-2.11%, 11.48%]. No subgroup presented less than 25% disability progression. These results show no statistically significant difference in disability progression of MB leprosy patients treated with U-MDT or R-MDT regimens.

(iv) Relapse

Four patients in the U-MDT group relapsed representing a relapse rate of 2·6 per 1000 patients per year of follow up (95% CI [0·81, 6·2] per 1000) during the active follow up period, which ended on April 30th, 2015. In the R-MDT group, supposing the same relapse rate, the expected number of relapses would be five, but no relapse was observed.

During passive follow up (May 1st, 2015-June 1st 2016) three MB patients in U-MDT and one in R-MDT group relapsed. It was difficult to define accurately the denominator to estimate

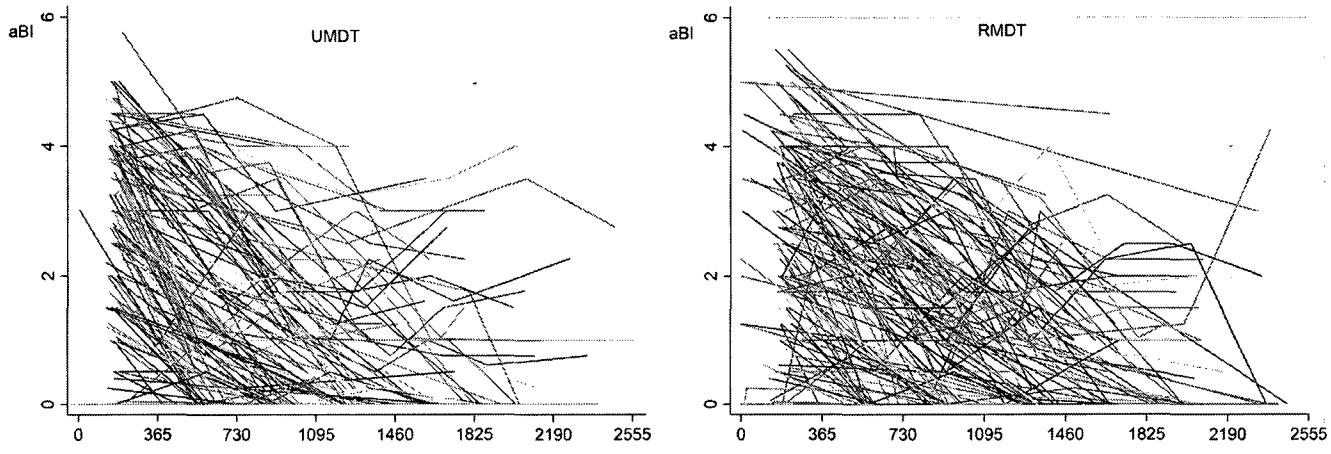

Fig 4. Observed average bacilloscopic index/aBI by time (days) for each multibacillary leprosy patient.

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the relapse rate when passive follow up time was considered. In order to overcome this, we did a sensitivity analysis, *i.e.*, we estimated the rate using the follow up person-years that results in an overestimation bias. The estimated rate of relapse for U-MDT group was 4.46 per 1000 people per year and for R-MDT 0.44 per 1000 people per year. This means that in the U-MDT group the overestimated relapse risk in ten years is 4.4%. As the relapse risk is surely lower than 4.4% in ten years, we consider the U-MDT relapse rate acceptable for use. Thus far, the recruitment centres participating in the U-MDT trial continue to follow up of patients.

Table 3 describes sociodemographic and clinical characteristics of the four MB patients from the U-MDT regimen who relapsed during active follow up. All of these patients had initial aBI $\geq$ 3·5 and were classified, according to Ridley Jopling, as lepromatous or borderline lepromatous leprosy.

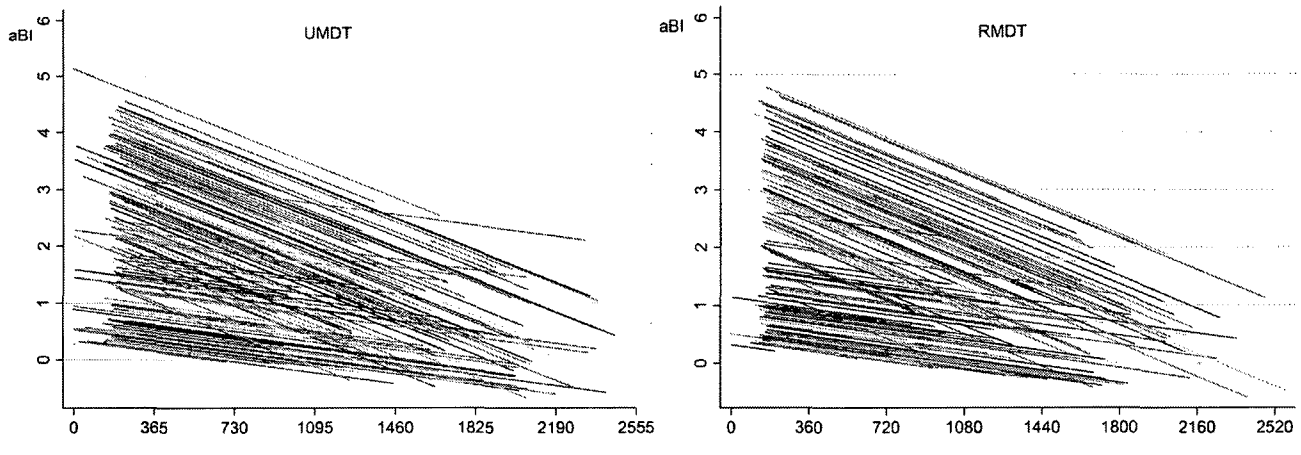

Fig 5. Adjusted average bacilloscopic index/aBI by time (days) for each multibacillary leprosy patient. *linear adjusted declining trend usually produces negative values as in this graph, although this is not biological plausible.

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Table 2. Analysis of bacilloscopic index decrease among multibacillary patients and parameters of the multilevel linear model with mixed effects.

aBI_t	Coefficient	Standard Error	z value	p value	95% Confidence Interval	
Treatment group	·00910	·0810	0·11	0·911	-·1496	·1677
Ln (Days of follow up)	-·0005	·000056	-9·56	0·000	-·00064	-·00042
Initial BI	2·6290	·1044	25·18	0·000	2·4244	2·8337
Days X initial BI	-·0010	·00008	-12·70	0·000	-·0012	-·00087

BI: bacilloscopic index; Random—effects Parameters: sd (constant) = 0·7567185 $CI_{95\%}$[0·6922–0·8272504]
sd (residual) = 0·78295 $CI_{95\%}$[0·746861–0·820779]

https://doi.org/10.1371/journal.pntd.0005725.t002

Discussion

In this randomized, controlled clinical trial, expert dermatologists with vast experience in leprosy, robust methodology, well-established follow up and high-level epidemiological analysis

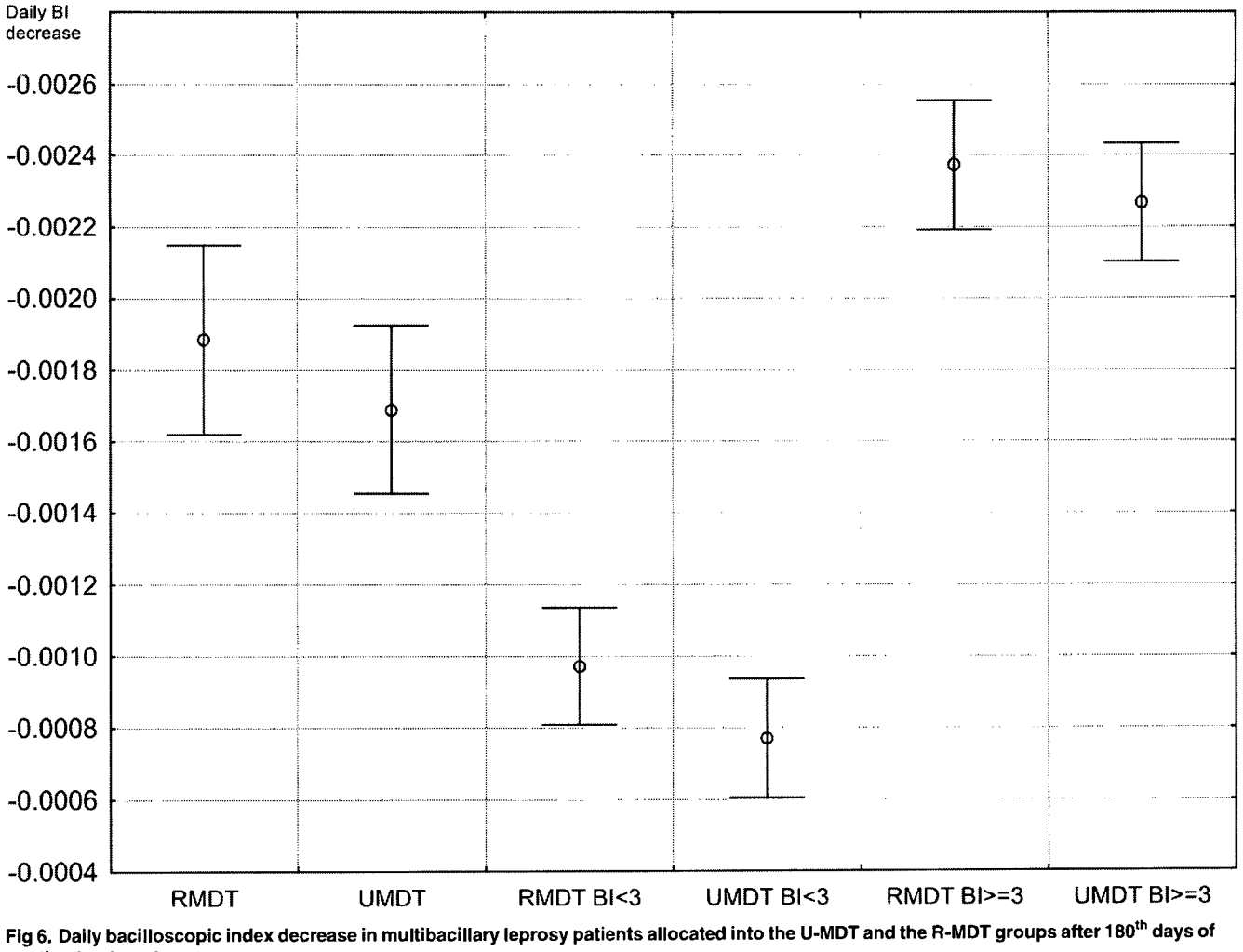

Fig 6. Daily bacilloscopic index decrease in multibacillary leprosy patients allocated into the U-MDT and the R-MDT groups after 180th days of starting treatment.

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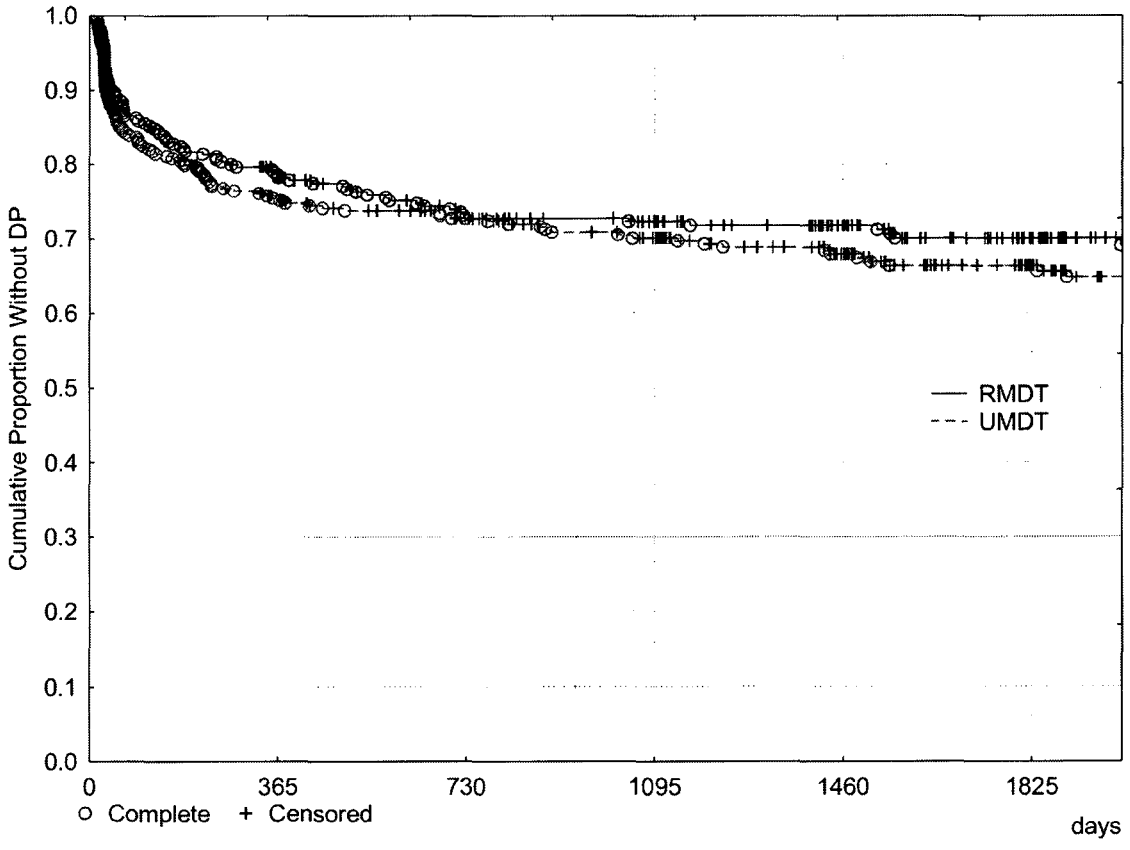

Fig 7. Cumulative proportion of MB leprosy patients without Disability Progression (Kaplan Meier curve).

https://doi.org/10.1371/journal.pntd.0005725.g007

were employed to compare the main outcomes observed between regular MDT and uniform MDT regimens. This comparison included the relapse rate, the frequency of leprosy reactions, the bacteriological index trends during treatment and follow up and disability progression.

The risk of relapse is considered the main outcome measure in a clinical trial and in leprosy, the reduction of treatment duration may raise the possibility of insufficient treatment that would result in very early relapses, similarly to what has been shown in four months tuberculosis treatment [11]. Our study found a higher rate of relapses in the U-MDT group, but without statistically significant difference compared with R-MDT. This rate is acceptable for leprosy control programs because the superior limit of the confidence interval is lower than 1%. However, we point out that the lack of an accurate, simple and standardized criterion for the diagnosis of relapse, limits any further comparison of results reported by different studies. Therefore, we consider that a precise estimate of the relapse rate after MDT is unlikely to be obtained, because relapses are rare events that may take place long after treatment conclusion. Additionally, accurate estimates of leprosy relapse require both large group of patients and long follow up after treatment. In this regard, considering the long evolution of leprosy, one potential drawback of our study may be the relatively short follow up, which does not allow the detection of late relapses cases. However, previous studies have reported a higher rate of early relapses compared to late events. A study with proper sample size showed that the risk of early relapses, defined as the ones observed before 5 years after treatment conclusion is higher than late relapse risk. Also, more than half of the total relapses were observed in the early period [12].

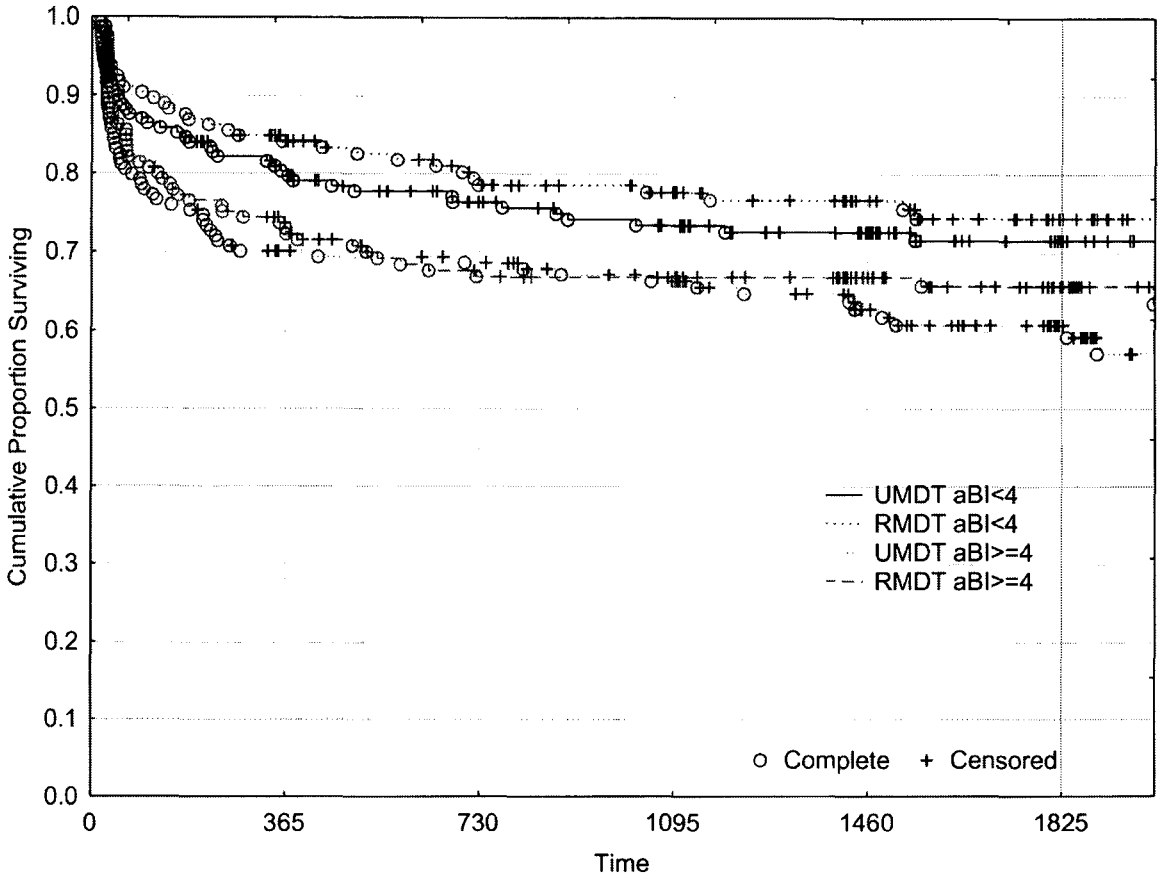

Fig 8. Cumulative proportion without Disability Progression of MB leprosy patients (Kaplan Meier curve).

https://doi.org/10.1371/journal.pntd.0005725.g008

One international open trial on U-MDT performed in India and published in 2008 [13] reported six relapses and all of them were considered early relapses. Three of them were observed at the first year, two at the second and one at the third year of monitoring. In this study, early relapses were diagnosed based only on clinical examination by primary care

Table 3. Socio-demographic and clinical characteristics of MB patients from the U-MDT arm that relapsed during active follow up period.

Case #	Age at diagnosis (years)	Gender	Date of U-MDT start (month/ year)	Ridley Jopling Classification at diagnosis	Relapse Date (month/ year)	Ridley Jopling Classification at relapse	Initial aBI	Lowest aBI/ date (month/ year)	aBI at Relapse
CE 0126	32	M	06/2007	BL	09/2011	LL	4.0	1.25 06/2010	4.0
CE 0188	20	M	09/2007	LL	11/2014	LL	3.5	3.0 07/2014	4.2
CE 0208	17	M	10/2007	LL	04/2015	LL	4.75	1.0 09/2011	4.0
AM 0014	33	M	04/2007	LL	04/2011	LL	4.5	0.25 07/2010	3.0

M: male aBI: average bacilloscopic index; BL:borderline lepromatous; LL: lepromatous.

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workers. The Chinese trial on U-MDT, published in 2015 that defined relapses based on skin smear results, reported one relapse observed at 13 months of follow up, among 144 leprosy patients monitored for up to six years [14]. In our open cohort pilot study for CRF test, among the 19 MB patients included, two relapsed ten years after ending U-MDT. Both patients were classified as LL, and upon starting U-MDT they presented BI = 2.75 and BI = 5.0 and at the time of relapse they had BI = 5.0 and BI = 3.75 respectively. These two relapse cases were not included in the statistical analysis of U-MDT/CT-BR. A recent publication from Bangladesh compared outcomes of two similar open cohorts, U-MDT-MB and R-MDT-MB and suggested that shortening the duration of treatment from 12 to six months did not increase relapse rates [15]. Therefore considering evidences of the significant occurrence of early *versus* late relapses, we can consider that our follow up was enough to detect early relapses, which according to published studies, may represent the majority of these events.

In the current study our definition of leprosy relapse was based on clinical, histopathological and bacterial data. Additionally, whole genome sequence analysis of *M. leprae* obtained from the initial and the relapse skin lesions did not show any association of relapse with drug resistance mutations and demonstrated that reinfection with a different *M. leprae* strain can occur in susceptible MB patients that remain in endemic area after the conclusion of MDT (Stefani et al, 2017 in press). The results from this recent study suggest that susceptible patients may be reinfected with a different strain of *M. leprae*, regardless of the duration of MDT for six or 12 months and the possibility of reinfection after treatment. It is recognized that the integration of leprosy control activities in general health care is challenging [16] but our results support that U-MDT may be used for leprosy control, as the control activities aim the elimination of infectious sources. Also, the acceptable relapse rate observed in the U-MDT can underscore the implementation of this simpler treatment regimen in the primary care and this measure may contribute to avoid potential relapses due to misclassification of patients.

Leprosy reactions need to be monitored since they are the main cause of permanent incapacities and handicaps. The development of leprosy reactions after MDT is often defined by patients as disease symptoms, interfering in their quality of life. The current study shows that the incidence of recurrent reactions was not associated with treatment duration. Our results indicated that the development of leprosy reactions and BI decrease were similar between the U-MDT and R-MDT groups. An observational study that compared the rate of reactions of MB patients treated for one or two years showed association between reaction frequency and treatment duration and with BI [17]. The frequency of leprosy reaction reported previously was lower than that reported by us, but their analysis considered the initial time of monitoring as the end of treatment and not the beginning of the treatment as in our study.

The predefined, regular follow up intervals adopted in our study may eventually have increased the probability of diagnosis of leprosy reaction, especially when compared to the monitoring in the field by primary care workers reported in India[13]. Also, we acknowledge that the loss to follow up of patients can represent a limitation in our study due to the long-term monitoring required in leprosy studies. However, despite patients' loss, our study follow up still included enough patients that allowed robust analyses. In addition, we cannot exclude the possibility of an over surveillance of U-MDT group compared to R-MDT during monitoring.

The development of disabilities after MDT is also a serious medical event and there is no gold standard for the evaluation of disability progression after leprosy diagnosis. The U-MDT group presented higher disability progression; nevertheless this difference was not statistically significant. It is worth mentioning that the disability progression was high in all treatment groups and subgroups. The definition of disability progression/DP used in our study although very specific, has low sensitivity as it is based on the appearance of neurological damage in a

previously normal limb or eye, but it is unable to detect damage of a previously normal nerve in the same limb. Our results showed that around 30% of the MB patients had DP after the beginning of treatment. In terms of disability progression, we found a small difference in the proportion affected, lower than 4%. However, our trial results highlight the extremely large proportion of patients that developed new disabilities under both R-MDT and U-MDT. We recognize that a proportion of neurologic damage progression after diagnosis higher than 30% can be clearly considered a poor clinical outcome. In this sense, we strongly recommend a consensus definition and criteria to estimate disability progression in leprosy. We also emphasize the need to include the evaluation of disability progression as part of evaluation of ongoing or new leprosy treatment.

A prior study on disability progression employing the increase of WHO disability grade or the Bechelli´s index showed a disability progression incidence rate of 6.5 per 100 person-years [18], indicating a risk of 27.75% in five years, a value close to our findings. Our results on disability progression provide evidences that the WHO target to reduce grade 2 disability at diagnosis is not a reliable measure of the total disability produced by the disease, as a significant percentage of MB patient will progress with further neurological lesions, regardless of the treatment duration of six or 12 months. The disability progression rate represents a main knowledge gap in leprosy management, *i.e.*, prevention and effective treatment of reactions, with effective prevention of further neurological damage after diagnosis. Clinical trials, including those with a Bayesian design [19], should address the main triggers of disability progression rate.

Kumar et al. [20] showed the cumulative risk of disability after 4 years of follow-up, estimating that only 10% of patients were free from disability at the end of this period. This study did not find statistically significant differences in disability progression between those who completed 1 year of treatment and defaulters with less than six months of treatment. As their results come from an observational study, the comparison of groups may have been biased, because patients with a better clinical response to the initial doses/months of treatment could have had a higher probability of non-compliance to the full treatment.

Our study employed multilevel analysis of BI decline which considered for each patient, the initial BI as the control BI, and estimated the mean of BI decrease as a function of time instead of the decrease of the mean BI for all patients, as used when a traditional linear regression of BI values against time is estimated. It is worth pointing out that these two approaches estimate different values for the decrease in time with the traditional regression overestimating it. Although the decline is greater for those taking R-MDT, compared to U-MDT users, these differences were not statistically significant in this model especially when BI decrease in U-MDT and R-MDT after 180 days of starting treatment was analyzed, considering the 95% confidence interval.

The U-MDT/CT-BR trial followed a robust scientific basis [21] therefore the lack of statistically significant differences in the main clinical outcomes of MB patients treated with U-MDT or R-MDT including the relapse rate, the frequency of reactions, the bacteriological index trend and the disability progression, support the adoption of U-MDT as part of a control policy for leprosy [22]. The U-MDT can potentially simplify the expansion of treatment coverage to all health entities and reduce the overall rate of relapses and it may also contribute to prevent under treatment of MB patients misclassified as PB. Additionally the adoption of U-MDT can help prevent the over treatment of PB patients misclassified as MB, receiving dapsone daily for six further months. Finally, we acknowledge the need of further clinical trials including the prevention and treatment of leprosy reactions, and the prevention of new neurological damage after MDT initiation.

Conclusion

Our results on the first randomized and controlled study on U-MDT, together with the results from three previous studies performed in China, India and Bangladesh, support the premise that U-MDT is an acceptable option to be adopted by leprosy endemic countries, in the field worldwide.

Supplementary file

CONSORT statements checklist

Supporting information

S1 Consort Checklist.
(DOC)

S2 Plan Statistical Analysis.
(DOCX)

S3 Protocol U-MDT-CT-BR.
(PDF)

S4 Ethical Approval.
(GIF)

S5 Data File With Codebook.
(XLSX)

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Six years' follow-up of multibacillary leprosy patients treated with uniform multi-drug therapy in China

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Abstract

Objective This study was conducted to evaluate the effectiveness of uniform multi-drug therapy (UMDT) in patients with multibacillary (MB) leprosy.

Methods Newly detected MB leprosy patients were treated with six months of UMDT as recommended by the World Health Organization (WHO). The effectiveness of treatment was evaluated by clinical status and skin smear tests.

Results At the start, 114 patients were recruited, examined, and treated. These patients were re-examined and followed annually for up to six years. A total of 75 (65.8%) patients completed six years of follow-up. Dropouts were attributable to death, severe drug reactions, and other reasons. The mean ± standard deviation bacteriological index (BI) of all patients decreased from 3.01 ± 1.50 before treatment to 0.02 ± 1.84 at the end of year 6, reflecting a mean annual decrease of 0.50. The rate of smear negativity in all patients was 98.7% at the end of year 6 of follow-up. A total of 53 leprosy reactions were observed. One patient relapsed 13 months after the cessation of treatment.

Conclusions A 6-month administration of UMDT is effective in MB leprosy patients. The changes in BI values and the frequency of leprosy reactions were similar to those cited in reports in the literature of patients treated with 1- or 2-year regimens of MDT. However, further research should be conducted to confirm the present results.

Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. The aim of chemotherapy is to kill all bacilli and then to allow the patient's immune system to clear them. In 1981, the World Health Organization (WHO) recommended that multi-drug therapy (MDT) for multibacillary (MB) leprosy patients should be administered for at least two years or, if possible, until skin smears show negative results.[1] In 1998, the WHO Leprosy Expert Committee further recommended that the period of administration of MDT in MB patients could be shortened to 12 months without increasing the risk for relapse.[2] In 2012, the WHO Leprosy Expert Committee again recommended that pilot trials of uniform MDT (UMDT) for all types of leprosy using a 6-month treatment regimen should be conducted.[3] The UMDT project resulted in worldwide debate, especially with regard to UMDT treatment in patients with MB leprosy. We have conducted a clinical trial within the UMDT project in Guizhou and Yunnan provinces in China under the auspices of the WHO since 2003. Here, we report the results of six years of follow-up in MB leprosy patients treated with the UMDT regimen.

Materials and methods

The study was approved by the Medical Ethics Committee of the Institute of Dermatology, Chinese Academy of Medical Sciences. Patients were recruited between November 2003 and July 2005. The criteria for recruitment required patients to be diagnosed with newly detected or relapsed MB leprosy, to be aged 14–65 years, to show a positive skin smear, and not to have undergone any treatment. Diagnoses of leprosy were confirmed in all patients by professionals working at county units for leprosy control or in a higher capacity. All patients agreed to take part in the study and signed a consent form. All patients were aware that they could withdraw at any time. The criteria for exclusion from the study included any of the following indications: (i) severe damage affecting liver or kidney function; (ii) severe anemia; (iii) psychiatric disease; (iv) severe illness; and (v) pregnancy.

Patients affected by the occurrence of adverse events were regarded as withdrawn. Other reasons for withdrawal included:

(i) severe leprosy reaction; (ii) migration to a remote area; (iii) death from other causes; (iv) dapsone allergy; (v) relapse; and (vi) refusal to participate in follow-up as a result of the stigma associated with the disease.

The UMDT drugs were provided by the WHO. Patients were treated with rifampicin 600 mg once per month, dapsone 100 mg per day, and clofazimine 300 mg once per month plus 50 mg per day for six months. The monthly administration of the drugs was observed by local health workers as stipulated by the study protocol. After the completion of treatment, all patients were followed up once per year by local health workers to check on the occurrence of a leprosy reaction or neuritis, and skin smear tests on at least four sites of skin lesions were performed by technicians working at county level to investigate any change in the bacteriological index (BI). The criteria indicating relapse referred to the presence of active skin lesions, an increased BI value, and findings of solid stained bacilli.

Patient data were collected using a special form distributed by the WHO and completed by local medical professionals employed by the county unit for leprosy control. Data were reported to the Institute of Dermatology. Data were first checked and then entered into a computer database to be analyzed by descriptive methods using SPSS Version 16.0 (SPSS, Inc., Chicago, IL, USA).

Results

A total of 114 MB leprosy patients were recruited between November 2003 and July 2005. Of these, 82 were male and 32 were female. The mean ± standard deviation (SD) age of the patients was 34.85 ± 13.30 years (range: 11–65 years). The mean ± SD BI at baseline was 3.01 ± 1.50, and 33 (28.9%) patients had a BI of ≥4.0. The rate of grade 2 disability was 22.8% (26 of 114 patients). Twelve (10.5%) patients had a leprosy reaction before the trial.

During the 6-year follow-up, 39 patients dropped out of the trial for various reasons. Six patients dropped out of the trial during the treatment phase, and 10, eight, six, six, one, and two patients dropped out during follow-up years 1, 2, 3, 4, 5, and 6, respectively (Table 1). Reasons for dropping out included diaminodiphenylsulfone (DDS) allergy, death, migration, severe leprosy reaction, relapse, and refusal to attend check-ups. Ten patients died during the study of malnutrition (n = 1), organ failure associated with advanced age (n = 1), alcoholism (n = 1), drowning (n = 1), suicide (n = 1), diarrhea (n = 1), pulmonary heart disease (n = 1), acute hepatitis (n = 1), and unknown causes (n = 2).

The average BI of all patients declined from 3.01 at baseline to 1.82 at the completion of treatment and subsequently to 1.01, 0.63, 0.39, 0.21, 0.05, and 0.02 at follow-up years 1, 2, 3, 4, 5 and 6, respectively. The annual decline in BI was 0.50. The rate of BI negativity across all patients rose from 0% at baseline to 23.3% at the end of treatment and subsequently to 33.7, 53.8, 70.1, 85.9, 94.6, and 98.7% at 1, 2, 3, 4, 5, and 6 years of follow-up, respectively. Only one patient showed a weakly positive BI at year 6 (Table 2).

A total of 53 leprosy reactions were observed during the trial, of which 21 were type 1 and 32 were type 2 reactions. Leprosy reactions were seen in 12 patients at baseline, nine patients during treatment, and 12, seven, four, four, three, and two patients at 1, 2, 3, 4, 5, and 6 years of follow-up, respectively. The highest frequencies of leprosy reactions occurred during treatment and within the first two years of follow-up. During the third year of follow-up and subsequently, the rate of leprosy reactions decreased gradually.

One patient relapsed 13 months after stopping the treatment. This patient had borderline lepromatous leprosy with an initial BI of 3.6. At the end of treatment, this patient's BI had decreased to 2.6. However, the patient presented many areas of erythema and nodules with infiltration on the face, trunk, and limbs at 13 months after stopping the treatment. The skin smear test was strongly positive, with a BI of 3.4, and showed many acid-fast bacilli on staining. The patient was confirmed as demon-

Table 1 Reasons for the withdrawal of patients from the study

	Follow-up time							
Reason for withdrawal	**During treatment**	**1 year**	**2 years**	**3 years**	**4 years**	**5 years**	**6 years**	**Total withdrawals**
Migration, *n*	2	4	1	3	3	1	1	15
Death, *n*	2	1	4	1	3	0	0	11
Severe leprosy reaction, *n*	0	5	2	1	0	0	0	8
DDS allergy, *n*	2	0	0	0	0	0	0	2
Refusal of check-up, *n*	0	0	0	1	0	0	1	2
Relapse, *n*	0	0	1	0	0	0	0	1
Total, *n*	6	10	8	6	6	1	2	39

DDS, diaminodiphenylsulfone.

Table 2 Changes in bacteriological index (BI) and incidences of leprosy reactions in multibacillary leprosy patients treated with uniform multi-drug therapy (UMDT)

	Before therapy	After therapy	Follow-up time after stopping UMDT					
			1 year	2 years	3 years	4 years	5 years	6 years
Patients, *n*	114	108	98	90	84	78	77	75
Patients with type 1 reaction, *n*	5	5	3	4	1	1	1	1
Patients with type 2 reaction, *n*	7	4	9	3	3	3	2	1
Total, *n* (%)	12 (10.5%)	9 (8.3%)	12 (12.2%)	7 (7.8%)	4 (4.8%)	4 (5.1%)	3 (3.9%)	2 (2.7%)
Patients with skin smear, *n*	114	86	83	80	81	78	74	75
BI, mean ± SD	3.01 ± 1.50	1.82 ± 1.40	1.01 ± 1.03	0.63 ± 0.90	0.39 ± 0.80	0.21 ± 0.54	0.05 ± 0.28	0.02 ± 1.84
Patients with negative BI, *n* (%)	0	20 (23.3%)	28 (33.7%)	43 (53.8%)	57 (70.1%)	67 (85.9%)	70 (94.6%)	74 (98.7%)

SD, standard deviation.

strating relapse and treated with routine MDT. The relapse rate was 0.06 per 100 patient-years (one per 1677 patient-years) during six years of follow-up.

Discussion

Along with improvements in skin lesions, BI values represent one of the most sensitive and objective indicators of the effectiveness of treatment for leprosy.

Sales *et al.*[4] reported 128 MB leprosy patients treated with WHO MDT for one year, in whom the BI decreased from 2.27 before treatment to 1.56 at the completion of treatment and to 1.03 at one year after the cessation of treatment. These authors also reported negative BI values in 31.9% of their 128 MB patients at one year after the completion of treatment.[4] Yu *et al.*[5] reported 149 MB leprosy patients in the same area as the present UMDT program in China, who were treated with two years of MDT, 77.2% of whom demonstrated a negative BI at four years after starting treatment. Li *et al.*[6] reported a series of 56 patients with newly detected MB leprosy, who were treated with MDT until skin smear results were negative, and cited a rate of negative skin smear results of 91.1% at five years after the initiation of treatment. In another study, Li *et al.*[7] also reported that 34 patients with newly detected MB treated with MDT until skin smear results were negative and showed a decrease in BI values from 2.0 before treatment to 0.01 at five years after the start treatment and a BI negative rate of 97.1%. Shen *et al.*[8] reported that 79 patients with newly detected leprosy treated with MDT until skin smear results were negative showed a decrease in BI from 3.01 before treatment to 0.02 at six years after the start of treatment and a BI negative rate of 92.0%.

We found changes in the BI of our patients after treatment to be very similar to those cited above. In our study, 114 MB leprosy patients treated with only six months of MDT achieved a decrease in BI from 3.01 before treatment to 1.82 at the end of treatment and 1.01 at one year after treatment, with a negative BI rate of 33.7%. At 42 months after the start of treatment, the negative BI rate was 70.1%. Even in comparison with the patients reported by Li *et al.*,[6,7] in whom MDT treatment continued until skin smear results were negative, the present findings show impressive rates of negative BI findings of 94.6% and 98.7% at five years and six years after treatment, respectively. These findings indicate that there was no difference in BI changes and rates of negative skin smear findings between patients treated with UMDT and those treated with MDT for one or two years.

However, Shetty *et al.*[9] reported that 16% of borderline lepromatous and lepromatous leprosy patients showed viable leprosy bacilli growth in a mouse foot pad test after 18 months of MDT. We speculate that those viable leprosy bacilli may represent leprosy persisters with a very low metabolic rate in the patient's body. The non-sterilizing immunity of a patient can kill these few viable bacilli. The very low relapse rate of leprosy patients treated with 12 months of MDT as recommended by the WHO since 1998 may resolve concern of a high relapse rate resulting from a few viable leprosy persisters.

The incidence of leprosy reactions during the course of the disease is also an indicator that can be used to evaluate the acceptance of a new regimen by patients. Sales *et al.*[4] reported that among 128 MB patients treated with MDT for one year, 71.9, 56.3, and 63.1%, respectively, of patients developed leprosy reactions during the first 12, 24, and 36 months after the initiation of treatment. In a similar study of UMDT in Brazil, the authors reported that patients with a BI of <3.0 showed a significant difference in reaction frequencies during the period between six and

18 months from the beginning of treatment and that the difference disappeared at two years after the start of treatment.[10] Feuth *et al.*[11] reported that among 94 MB leprosy patients treated with MDT for two years, 41% of patients developed type 2 leprosy reactions within one year of the start of treatment.

In our study, a total of 53 leprosy reactions were observed during the trial. Most leprosy reactions occurred during treatment and within the first two years of follow-up. During the third year of follow-up and afterwards, the rate of leprosy reactions decreased gradually. We found that the total incidence of leprosy reactions in our patients was lower than that reported by Sales *et al.*[4] and that the incidence of type 2 leprosy reactions was also lower than that reported by Feuth *et al.*,[11] even including the eight patients who withdrew from the study during follow-up years 1, 2, and 3 for reasons of severe reactions.

However, the incidence of type 1 leprosy reactions was reported to be 14.6% within 42 months after the start of treatment in 89 MB patients treated with UMDT, which is significantly higher than the rate of 3.4% in 149 MB patients treated with two years of MB-MDT and observed within 48 months of the start of treatment in the same area in China.[5] Although there was no significant difference in the incidences of type 2 leprosy reactions between patients treated with UMDT and those treated with routine MDT, the higher incidence of type 1 leprosy reactions among patients treated with UMDT requires attention, and its mechanism should be studied.

In the present study, other than that in the one patient who relapsed at 13 months after the cessation of treatment to give a relapse rate of 0.06 per 100 patient-years, no relapse was observed during six years of follow-up. This is very positive information. The only possible mechanism that may explain this phenomenon is that the 6-month UMDT regimen has a bactericidal efficacy equivalent to that of a 1- or 2-year MB-MDT regimen and kills almost all viable leprosy bacilli harbored in the patient's body. However, further research is required to confirm these results.

In conclusion, the preliminary results of this UMDT trial show that the UMDT protocol facilitates rapid bactericidal activity, a permanent decline in BI, a low relapse rate, and an acceptable frequency of leprosy reactions. The effectiveness of UMDT is similar to that of 1-year MDT.

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Outcome of 6 months MBMDT in MB patients in Bangladesh- preliminary results

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Summary

Introduction: Duration of leprosy treatment remains long and difficult to complete in resource poor areas. Studies suggest that shortening duration of therapy for MB patients to 6 months may be possible.

Methods: New MB patients in 2005 in two NGO projects in Bangladesh were treated with 6 months WHO MB MDT and the rate of relapse and fall in BI on slit skin smear during follow up to date were compared with a control group treated for 12 months the previous year.

Results: 1612 patients were enrolled in the trial, and the average duration of follow up was over 7 years after diagnosis. During 11,425 PYAR of follow-up, no relapses were detected, by bacteriological or clinical criteria, in the 918 patients in the 6 months MB MDT group, nor in the 694 patients in the control group. Rate of decline of BI in those who were smear positive was not significantly different between groups.

Conclusion: The data does not suggest that shortening duration of treatment from 12 months to 6 months MDT for MB leprosy patients leads to increased rates of relapse.

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Introduction/Background

Triple drug therapy for Multi-bacillary (MB) leprosy patients was recommended by WHO as routine first line treatment in 1981.[1] Originally it was given to all leprosy cases with initial skin smear $>1+$ at any one site, or those clinically classified as borderline borderline, borderline lepromatous or lepromatous (BB, BL, LL). The minimum duration of treatment advised was 24 months, but continuing 'until smear negative' was recommended. Over the years the definition of multibacillary has changed to include any smear positive case.[2] The standard duration of multidrug therapy (MDT) for MB cases was fixed at 24 months, irrespective of smear status at that point, and then was reduced to 12 months.[3–5] Outcomes at a population level have remained good, although some concern has been raised about the adequacy of 12 months MBMDT for initially highly smear positive cases.[6,7] In 2002, it was proposed to test a shorter regimen in MB cases with a view to offering the same 6 month regimen of three drugs to both paucibacillary (PB) and MB cases, as 'uniform multidrug therapy (U MDT)'.[8–10]

We tested the impact of the 6 month MBMDT regimen (compared with the standard 12 month regimen) on newly diagnosed adult leprosy patients in two leprosy control programmes in Bangladesh who are being followed for 10 years after diagnosis. Effectiveness of 6 months MBMDT treatment was to be assessed in terms of rate of fall of bacteriological index (BI) in initially smear positive subjects (proxy outcome measure, to reflect bacteriological killing and clearance) and of rate of relapses within the observation period (clinical outcome). In addition subjects were assessed in terms of morbidity and disability outcomes as indicated by occurrence of reactions and changes in nerve function/WHO disability grade. Information on pattern of reactions and residual morbidity data will be reported in a separate paper.

Here we present a preliminary analysis of rates of relapse and fall in BI in the two groups, at which point 8 years of follow-up information was due in all patients, and a small proportion had 10 years follow-up data available. This analysis has been completed to help inform current high-level discussions on appropriate duration of MDT for leprosy patients.

Methods (Subjects etc)

The study was conducted jointly by Damien Foundation Bangladesh and The Leprosy Mission International, Bangladesh, which are both partners in the National Leprosy Control Programme, and between them cover 16 districts (total population of 39 million) in central and northern parts of the country. The regimen to be tested, for adults over 45 kg, consisted of standard WHO-recommended MBMDT, i.e. monthly rifampicin (600 mg) with monthly clofazimine 300 mg (supervised), plus daily dapsone 100 mg and clofazimine 50 mg (self-administered) for a period of 6 months, with appropriately lower doses for low body weight individuals. Comparison subjects received the same drugs and dosages but for 12 months. 6 month and 12 month courses were to be completed within a maximum 9 months and 18 months respectively as per standard WHO treatment completion requirements.

New cases of MB leprosy were considered eligible if they were over 15 years old, had no known contraindications to the drugs, and consented to participation after being given full information about the trial. All cases were diagnosed by leprosy trained health workers and diagnosis was confirmed by a medical officer. Eligible subjects were enrolled sequentially in

the study group to receive 6 month MBMDT when they were diagnosed as new cases of MB leprosy in the local clinics from early in 2005. Enrolment continued until the required number was reached. Any subjects who did not consent were given standard 12 month MBMDT treatment.

The sample size required was determined pragmatically as a minimum of 1300 subjects, a number sufficient to detect a rise from a predicted baseline rate of relapse of 1% for 12 months MBMDT over 10 years to an estimated relapse rate of 5% in those treated for 6 months only, with confidence intervals of 95%.

The comparison group included all consenting eligible MB patients registered as new cases in the previous year (2004). Both groups were given the same routine care and active follow-up by the same health care staff according to standard operating protocols in place. Subjects were seen monthly until released from treatment, then were reviewed annually, either at the clinic or in their own homes. At each time point they were clinically examined including assessment of nerve function. Skin smears were done at diagnosis, at RFT (whether after 6 or 12 months treatment) and bi-annually from 12 months after diagnosis. Any subject suffering 'late' reaction (more than 5 years after diagnosis) was carefully examined at the time of occurrence, if necessary with a skin biopsy performed, to exclude the possibility of relapse. If subjects failed to attend clinic, staff repeatedly attempted to contact them by mobile phone or home visits (within a week if still under treatment, or within 3 months if already RFT). If a skin smear was not done for any reason at the due time, it was scheduled to be done at the next annual review.

Time points/periods are calculated from the point when treatment with MDT was begun (not from RFT) because of the different lengths of treatment regimens. It is assumed patients' bacteriological status will begin to improve as soon as they start MDT. The time-specific risk of reactional episodes is also likely to be related to start of treatment rather than to end of MDT.

MB Classification was assigned if patients had clinical signs of leprosy with more than five skin lesions, more than one nerve affected, or were skin smear positive at any one site, according to national guidelines, which follow those of WHO.[4] Relapse was defined as: "For originally smear negative MB patients: smears becoming positive or new clinical lesions of leprosy (both skin and nerve lesions) appearing at any follow-up. New clinical lesions should be carefully differentiated from signs of a reaction; trial of steroids was advised to clarify this issue. For previously smear positive patients: average B.I. increasing by at least 2+, compared with previous value. Histopathology of new active skin lesions was also required for diagnosis of relapse".[11–13] No subject was to be diagnosed as relapse without two leprosy specialists independently examining the case and agreeing that he/she met the criteria.

The trial was approved by Bangladesh medical research council (BMRC/ERC/2004-7//1267, dated 12.04.05).

Results

Enrolment continued up to about 1600 subjects to ensure that there would be adequate numbers remaining if loss to follow-up proved to be high. 1626 Subjects were finally enrolled of which 13 were excluded from the analysis as maximum Bacteriological Index (BI) at diagnosis was unavailable, and one was excluded as there was no data: leaving 918 for 6 months' regimen and 694 for 12 months' regimen.

Table 1. Total subjects enrolled according to site and regimen

	Project site		Regimen group		
	DBLM	DF	6 m cohort	12 m cohort	Total
n	554	1059	918	694	1612*
Male (%)	408 (73·8)	748 (70·6)	673 (73·3)	483 (69·6)	1156 (71·7)
Female (%)	145 (26·2)	311 (29·4)	245 (26·7)	211 (30·4)	456 (28·3)
Mean age (SD)	38·1 (14·2)	40·5 (15·4)	40·0 (14·7)	39·2 (15·4)	39·7 (15·0)

*Excludes 13 for whom no initial BI results.

There is no statistical significant difference between 6 m and 12 m group for sex ratio (chi squared 2 (1) = 2·5514, $P = 0·110$), nor for age distribution ($P = 0·2919$).

The two groups (6 months' and 12 months' regimen) were similar in terms of age/sex distribution and other characteristics such as WHO disability grading. There was no major difference between subjects in each of two projects at entry into the trial (Table 1), although follow up proportion by project varied slightly (average follow up in DF and DBLM respectively was 6·4 and 8·3 years).

At last recorded assessment we have follow-up of a total of 14721 person years at risk (PYAR) To date mean duration of follow up is 7·02 and 7·18 years respectively for 6 and 12 month regimes, 25% subjects have completed 9 years follow up, and 7% have completed 10 years follow up (Table 2).

Subjects were classified according to their initial skin smears (maximum BI at any one site) as negative ($n = 941$), low positive (defined as BI = 1+ to 3+) ($n = 291$) or high positive (BI = 4+ to 6+) ($n = 380$). The proportion with initially negative smears was slightly higher in 6 m group (Table 3), but the difference was not statistically significant. High positives were 56·63% of all positives at diagnosis.

Withdrawals were classified as early or late. The 72 early withdrawals (before RFT) were mainly due to dapsone hypersensitivity syndrome (or failure to complete treatment within the

Table 2. Follow-up periods: when last seen for assessment and last smear done (subjects known to be withdrawn have not been deducted from the denominator)

Years from diagnosis	Months from diagnosis	Number of subjects last seen at this time point	Percentage of total enrolled
0	0	144	8·93%
0·5	6	31	1·92
1	12	134	8·31
2	24	12	0·74
3	36	154	9·55
4	48	23	1·43
5	60	156	9·68
6	72	31	1·92
7	84	231	14·33
8	96	179	11·10
9	108	404	25·06
10	120	113	7·01
Total subjects		1612	

Table 3. Bacteriological status at entry (combined entry)

Initial smear result	6 m cohort	12 m cohort	total
Negative	554 (60·35%)	387 (55·76%)	941 (58·34%)
Low positive (1+ to 3+)	171 (18·63%)	120 (17·29%)	291 (18·05%)
High positive (4+ to 6+)	193 (21·02%)	187 (26·95%)	380 (23·57%)
All positive	364 (39·49%)	307 (44·23%)	671 (41·69%)
	$n = 918$	$n = 694$	$n = 1612$
Mean BI (SD)	1·31 (1·88)	1·61 (2·05)	1·43 (1·96)

Difference between proportion negative in each group not statistically significant: $P < 0{\cdot}064$, chi squared = 3·42.

specified time frame). The 199 later withdrawals were for a variety of reasons including 132 deaths and one withdrawal for a protocol error. A small number of subjects were 'lost to follow-up', without being formally withdrawn for a specified reason (usually this appeared to be because the family had left the district). Overall losses to date were 16·8% in the 6 month group and 16·6% in the 12 month group.

The numbers who died were 79/918 (8·6%) and 53/695 (7·6%) in the 6 month and 12 month cohorts respectively which is not a statistically significant difference ($P = 0{\cdot}477$). The high death rate is thought to be related to the advanced age of many of the subjects (at entry mean age = 39, hence by completion of 10 years follow up mean age = 49 years), considering the concurrent life expectancy in rural Bangladesh. For a subset of those who died (all 39 from two districts of RHP area, of which 17 were in the 12 month group and 22 in the 6 months group), enquiries were made about cause of death. In this subset, only three deaths appeared to be directly related to leprosy, anti-leprosy treatment or treatment of complications such as reaction (three died after prolonged steroid treatment, in two cases for chronic ENL reaction and in one case for reversal reaction).

To date no subjects seen in follow-up have been confirmed as cases of leprosy relapse according to our specified criteria. Fifty-eight subjects who were noted to have had one or more episode of reaction/neuritis more than 5 years after diagnosis, were specifically assessed by a medical officer at the time for evidence of relapse, in addition to routine annual follow-ups. One subject (originally highly smear positive and in 6 month group) had a smear report of 2+ at 72 months' follow-up, although his previous smear report at 48 months was negative. The patient had no clinical signs of relapse then nor at later assessments and subsequent smears were all negative. At 72 months his BI was still falling in comparison with previous positive smear results, and it is possible that the 48 month smear result might have been a false negative.

Except in that one subject, in no case did a negative smear become positive after RFT. Amongst the subjects who were initially smear-positive, most became negative within 5 years, and all but two became negative within 8 years. There is no significant difference in medium and long-term, for any initial smear status between those who had 6 months and those who had 12 months' MDT, in regard to the rate of fall of BI when the two regimens are compared (Figures 1 and 2), nor in the proportion of smears becoming negative (Table 4).

However, there is evidence that in the short term (at 12 months' follow-up) there is a faster fall in positivity rate, for the 6 month regimen, in the initially low smear positive group to 29·5% still smear positive compared with 43·7% in the 12 months' group ($P = 0{\cdot}019$). Also, the small percentage found positive at 12 months' follow-up in those initially smear

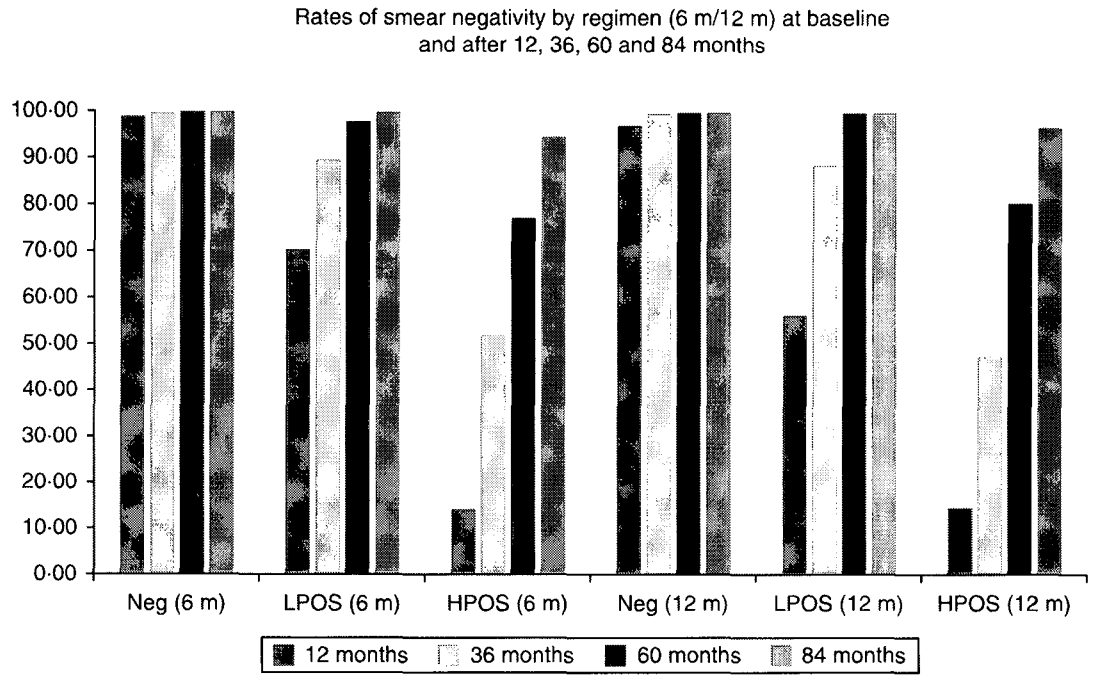

Figure 1. Progress to smear negativity for two regimens depending on baseline smear status. *The chart shows the percentage of assessed smears which were negative, in the negative, low positive (1–3) or high positive (4–6) smear subgroups within the alternative 6 and 12 months (6 m and 12 m) MDT regimens, at each of 4 time points during follow-up – after 12 months, 36 months, 60 months and 84 months of follow-up.*

negative was higher in the 12 month MBMDT group than the 6 month group (2·8% vs 1·0%; $P = 0{\cdot}05$). A possible explanation for these differences is an improvement in smear testing quality following commencement of the study.

Discussion

Success of an MDT regimen in leprosy can be assessed by two sets of criteria: the bacteriological response and the clinical outcome. Bacteriological index is a proxy outcome measure which reflects both killing of bacteria and clearance from the body. Level of BI is known to be associated with risk of relapse (and also risk of ENL reaction). Any clinical relapse is assumed to be due to multiplication of endogenous bacteria not killed by the chemotherapy (although new infection from an external source is possible). Clinical outcome is also assessed by morbidity in terms of episodes of immunological reaction, amount of nerve damage sustained, and/or final 'disability grading'. The likelihood of success according to both criteria may depend on the initial bacterial load as well as the sensitivity pattern of the bacteria and the duration of treatment.

LIMITATIONS OF STUDY

This study was not a randomised controlled trial and neither subjects nor staff were blinded to treatment regimen, however both groups received similar management and lived in the same social/epidemiological situation. Moreover the profile of two cohorts shows them to be broadly comparable in terms of age, sex ratio, proportion smear positive and WHO Grade at diagnosis. There was a slightly higher proportion of smear negative cases in the 6 month

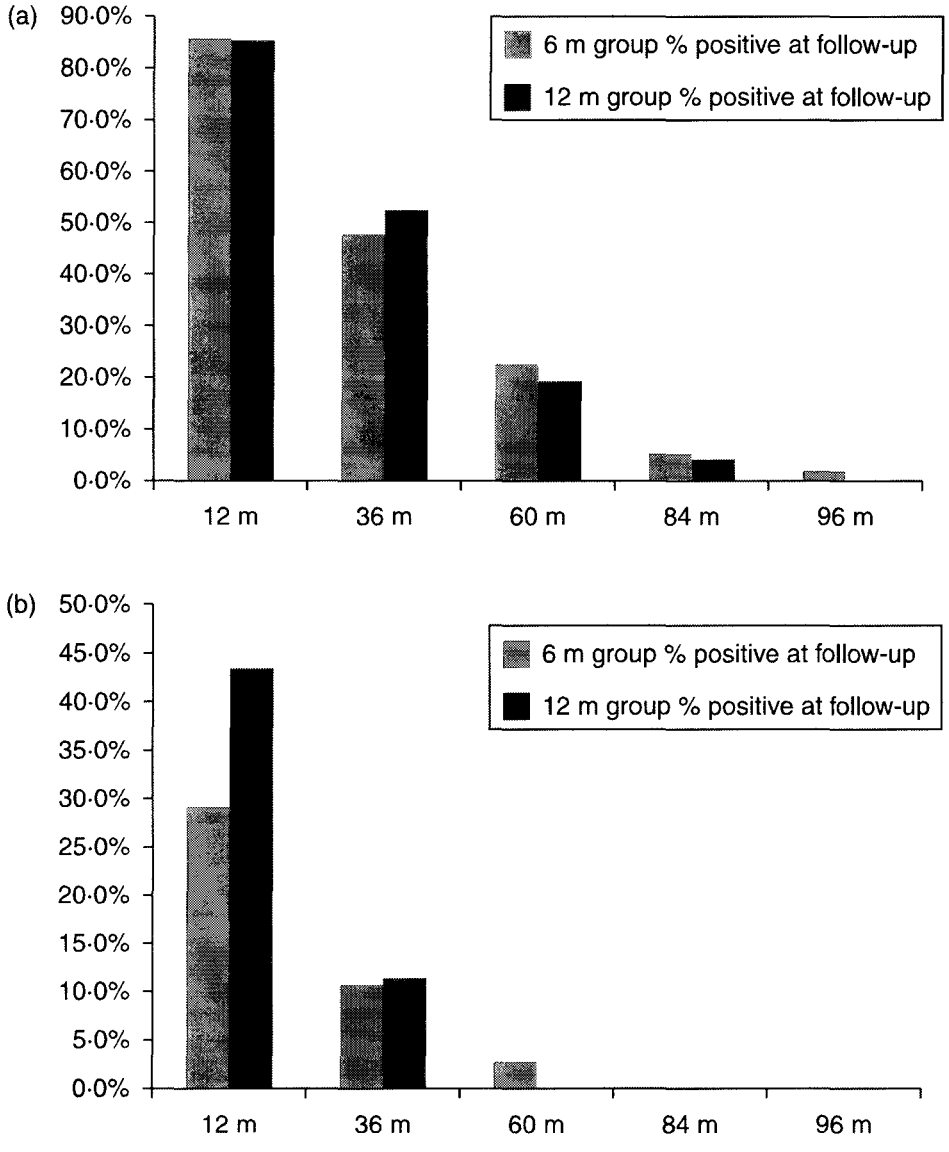

Figure 2. (a) Rate of decline of BI in 6 m versus 12 m group. Initially high positive cases. (b) Rate of decline of BI in 6 m versus 12 m group, Initially low positive cases.

group than in the 12 month group: this may have occurred because subjects who knew their smear was positive could have been more likely to refuse participation in the trial. Separate analysis of smear positive and smear negative cases partially offsets this disadvantage.

It is possible that the introduction of better quality control for skin smear readings, after commencing the study, had a small effect on bacteriological results; this is more likely to result in a decrease of false negatives rather than the reverse.

For pragmatic reasons we did not attempt to undertake a randomised controlled trial: not least because it would have been difficult to obtain placebo MDT packs and would have entailed a long delay before starting the study.

The duration of follow up might not be long enough to detect all relapses. However a 'relapse' due to inadequate treatment (e.g. if 6 mpnths' MDT was not sufficiently effective) might be expected to present earlier than one due to endogenous 'persisters' (dormant form of *M. leprae* remaining in the body despite a complete course of chemotherapy to which they are expected to be sensitive). Relapses which occur very late may be attributable to re-infection,

Table 4. Bacteriology at different time points (based on maximum smear at baseline)

	6 m cohort						12 m cohort						
	Time point from diagnosis	neg	pos	% pos Of known	n/a	total	Time point from diagnosis	neg	pos	% pos Of known	n/a	total	Statistically significant or not, between 2 cohorts
Initially smear negative	At 12 m	496	5	**1·05%**	53	554	At 12 m	311	9	**2·8%**	0·7	387	P = 0·050
	At 36 m	477	2	**0·4%**	75	554	At 36 m	328	1	**0·3%**	58	387	NS
	At 60 m	424	0	**0**	130	554	At 60 m	294	0	**0**	93	387	NS
	At 84 m	346	0	**0**	208	554	At 84 m	242	0	**0**	145	387	NS
	At 96 m	304	0	**0**	250	554	At 96 m	189	0	**0**	198	387	NS
Initially low positive	At 12 m	110	46	**29·5%**	15	171	At 12 m	58	45	**43·7%**	17	120	P = 0·019
	At 36 m	137	16	**10·5%**	18	171	At 36 m	93	12	**11·4%**	15	120	NS
	At 60 m	134	3	**2·2%**	34	171	At 60 m	94	0	**0**	26	120	NS
	At 84 m	109	0	**0**	62	171	At 84 m	87	0	**0**	33	120	NS
	At 96 m	92	0	**0**	79	171	At 96 m	70	0	**0**	50	120	NS
Initially high positive	At 12 m	25	149	**85·6%**	19	193	At 12 m	24	139	**85·3%**	24	187	NS
	At 36 m	84	77	**47·8%**	32	193	At 36 m	78	86	**52·4%**	23	187	NS
	At 60 m	112	33	**22·7%**	48	193	At 60 m	116	28	**19·4%**	43	187	NS
	At 84 m	109	6	**5·2%**	78	193	At 84 m	118	5	**4·1%**	64	187	NS
	At 96 m	102	2	**1·9%**	89	193	At 96 m	88	0	**0**	49	187	NS

although at present there is no convenient method of differentiating relapse due to an endogenous source from relapse due to new infection from an external source.

Considering the limited long-term data on incidence of relapse amongst large cohorts of patients treated with 12 or 24 month MBMDT, we believe that a planned follow-up duration of 10 years in this study reasonably balances the probability of finding relapse in relation to the trouble for patients and workload for staff. After 8 years many patients seen for assessment have been reluctant to continue with annual follow-up because they considered themselves 'cured' of leprosy. The percentage of missed assessments in some years is rather high, but if a subject was seen in the subsequent year and found to be 'not relapsed', it was assumed that he would not have shown signs of relapse in the previous year. If any smears were missed at due time (bi-annually) attempts were made to take another smear as soon as possible. Follow-up proportions were better in the 6 month than in the 12 month group, which may reflect the greater confidence of the subjects who had standard treatment leading them to avoid annual assessments, whereas subjects who received only 6 months' MDT may have felt more anxious about the possibility of late complications. Alternatively, staff may have been more diligent in follow-up of those known to have had only 6 months' MBMDT. The average duration of follow up to date is higher for the 12 months' group as they were enrolled earlier.

The examples given above of one subject with an unexplained negative smear result at 48 months' follow-up, and the small percentage of patients initially smear negative but reported smear positive at 12 months' follow-up (14/721 = 1·9%) (whose smears subsequently became negative without further MDT) illustrates the inherent limitation of the skin smear as an indicator of activity of the disease. Even in trained hands, a slit skin smear may occasionally give a false negative result on account of choosing a different site, faults in smearing (blood staining) or fixing, the quality of the stain, or technician error in the reading. Less often a false positive may be reported. It is important to consider the whole picture (clinical assessment of skin and nerve lesions, plus histology if possible) in deciding about a suspected relapse and not rely entirely upon a single smear result. Similarly when smears are used for monitoring response to treatment, a low positive BI at RFT time in a patient whose smear was reported negative at diagnosis but is clinically improved may not indicate treatment failure.

It is possible that we failed to detect a low relapse rate (or a small difference in bacteriological responses) because the number of subjects enrolled was too few. Larger population-based studies in future would be advisable. As we had no data on which to make the calculations more reliable we aimed for a large enough cohort to detect a five-fold difference in relapse rate over 10 years, if the baseline rate of relapse for 12 months' MBMDT was about 1%.[15] This was made on the pragmatic assumption that a rate of relapse of less than 5% might be acceptable at a population level if the duration of treatment could be shortened by 50%. An alternative design would be to use a 'non-inferiority' standard of calculating sample size.

A relatively low percentage of follow ups at end of study (40·1% were not seen after 5 years follow-up, but this includes people formally withdrawn) might have meant we missed a few 'relapse suspects'. Strenuous efforts are in progress to see as many of these as possible at the final 10 year follow-up. However, since there are almost no other leprosy services in our districts outside of those supported by our two NGOs, and government health staff routinely refer leprosy cases to our NGO services, we believe that anyone presenting with relapsed leprosy within their home area would have come to our attention. In addition it is national policy for any suspected leprosy relapse to be referred to a specialist centre for assessment,

and the study was widely advertised at national leprosy coordination meetings. So we can expect that any relapse cases among our subjects who presented elsewhere in the country should have been referred to the DBLM hospital referral centre (a Leprosy Mission Project), where medical officers were informed about the study.

In regard to relapse, it could be argued that PYAR is best calculated from completion of treatment rather than diagnosis. In this study, such an approach would decrease the overall years of follow-up, but would not alter the conclusions since no relapses were seen in either treatment or control group. As mentioned above, missed years can be ignored where a follow up assessment shows no relapse, however this assumption may not stand for reactions, where self-healing prior to the next assessment may have occurred, as documented in prior studies such as TRIPOD 3.[16]

Comparison with other reported studies: To date most studies published have not had very long follow up. Some studies have very low numbers. There are problems in comparison as some used different criteria for classification (e.g. all smear positive cases, and only those, were classified as MB as opposed to use of number of skin lesions in classification), and some were hospital-based rather than in the community. Not all authors performed/reported regular skin smears. Most authors count follow-up from time of RFT rather than from time of diagnosis. We consider the latter to be more logical, particularly in relation to reactional episodes and fall in BI. Although our method would have tended to underestimate relapse risk compared to the former, this is immaterial since we had no relapses in either group. Authors have different ways of describing the fall in bacteriological index over time and the temporal pattern of reactions, as well as using different criteria for diagnosis of relapse. Since diagnosis of relapse is a key issue in regard to studies of outcome of chemotherapy, there is a need for standardisation of criteria. This issue is discussed well by Kaimal.[17]

Preliminary results from the WHO-sponsored UMDT trial were reported after 8 years follow-up of 5000 cases: outcome was said to be 'favourable', but it is unclear what this means.[18] Another preliminary report[19] claimed that UMDT was 'safe and effective', since after 4 years follow up of 1302 MB cases (and 3396 PB cases) after UMDT, there had been only six relapses (at 13–28 months). Shen[20,21] reported from a study in China, out of 114 smear positive MB patients followed up for 6 years after UMDT, there was one relapse at 13 months after RFT (a case who had been initially 3·6+). Penna[22,23] in Brazil found in a Randomised Controlled Trial of UMDT, over 1366 PYAR (max 5·2 years follow up), only one relapse (at 4·5 years) out of 323 who had received UMDT.[22] In the same trial after 2139 PYAR, with a maximum 6·6 years follow up, a second relapse was found.[23] Both subjects were initially Highly Smear Positive cases. Kroger[24] reported four 'clinically confirmed relapses', from amongst 1136 MB cases (39% of all 2912 subjects in a UMDT trial).

So far, it seems from these and our studies, that the relapse rate after UMDT /6 months' MBMDT for MB cases is very low and not much higher than the rate for routine MBMDT of 12 months' duration.

Regarding Smear results: Shen[20] found that amongst 75/114 initially smear positive cases given UMDT (including 21 with BI $>$ 3+) 73·% and 98·7% respectively were smear negative at 3·6 and 6 years of follow-up after RFT. In an open label Randomised Controlled Trial, Penna[23] showed that amongst 613 MB cases (323 on UMDT for 6 months and 290 on 'Routine' MDT for 12 months), there was no statistically significant difference in fall of BI. Moreover the same was true if they analysed separately cases with BI = 1+ to 3+ or BI = 4+ to 6+ (using regression coefficient over time to assess fall in BI in each case rather than the mean of BI in all cases).

These outcomes are consistent with our findings, where most were smear negative by 5 years, and all but two by 8 years.

Whether or not the same favourable results would occur if 6 months' MBMDT was given as routine treatment for MB leprosy in an integrated leprosy control programme, as we obtained in two well-staffed research-orientated projects, is open to question. Our subjects had documented good compliance which may not be achieved under less stringent field conditions. It is possible that the 6 months' regimen would be less robust than a 12 month regimen, and taking the 6 months' medication over a longer period (e.g. 9 months) might be less effective. The need for careful monitoring of subjects for leprosy reaction or nerve function impairment during and for at least 2 years after 6 months' MB MDT, is also an important consideration; there may be an increased disability risk to subjects receiving a shorter course of chemotherapy.

Conclusion

While further follow up to 10 years is pending, the early evidence from this trial of 6 months' treatment for 918 MB leprosy patients after more than 7 years follow-up on average is that there is no excess of relapses compared with a similar cohort of 695 patients treated for 12 months. Similarly, the bacteriological response measured by rate of fall in BI in smear positive cases shows no delay in fall in the 6 months' group, and no relapses were seen in any smear positive (or smear negative) cases. Notwithstanding limitations of this pragmatic open study with an historical control group, this study provides further support to other emerging studies that 6 months' MB MDT could be cautiously recommended for use in all cases of MB leprosy where follow-up with quality skin smear testing is possible.

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Responsibilities

Dr Salim, Dr Withington and Dr Butlin conceived and designed the study, and organised funding and permissions. Dr Maug, Dr Pahan and Dr Butlin aided by Khorshed Alam implemented and oversaw the work throughout most or all of the 10 years, Dr Nicholls undertook statistical analysis. All authors shared in preparing the paper. Dr Butlin is guarantor.

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International open trial of uniform multidrug therapy regimen for leprosy patients: Findings & implications for national leprosy programmes

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***Background & objectives*: Uniform therapy for all leprosy patients will simplify leprosy treatment. In this context, we evaluated six-month multidrug therapy (MDT) currently recommended for multibacillary (MB) patients as uniform MDT (U-MDT) in a single-arm open trial under programme conditions. Primary objective was to determine efficacy to prevent five-year cumulative five per cent relapse. Secondary objectives were to assess acceptability, safety and compliance.**

***Methods*: Newly detected, treatment-naive leprosy patients were enrolled in India (six sites) and P. R. China (two sites). Primary outcome was clinically confirmed relapse of occurrence of one or more new skin patches consistent with leprosy, without evidence of reactions post-treatment. Event rates per 100 person years as well as five-year cumulative risk of relapse, were calculated.**

***Results*: A total of 2091 paucibacillary (PB) and 1298 MB leprosy patients were recruited from the 3437 patients screened. Among PB, two relapsed (rate=0.023; risk=0.11%), eight had suspected adverse drug reactions (ADRs) (rate=0.79) and rate of new lesions due toreactions was 0.24 (n=23). Rates of neuritis, type 1 and type 2 reactions were 0.39 (n=37), 0.54 (n=51) and 0.03 (n=3), respectively. Among MB, four relapsed (rate=0.07; risk=0.37%) and 16 had suspected ADR (rate=2.64). Rate of new lesions due to reactions among MB was 1.34 (n=76) and rates of neuritis, type 1 and type 2 reactions were 1.37 (n=78), 2.01 (n=114) and 0.49 (n=28), respectively. Compliance to U-MDT was 99 per cent. Skin pigmentation due to clofazimine was of short duration and acceptable.**

***Interpretation & conclusions*: We observed low relapse, minimal ADR and other adverse clinical events. Clofazimine-related pigmentation was acceptable. Evidence supports introduction of U-MDT in national leprosy programmes. [CTRI No: 2012/ 05/ 002696]**

Key words Chemotherapy - leprosy - uniform multidrug therapy

The mainstay of leprosy treatment until 1984 was dapsone monotherapy. Although it resulted in reduction of leprosy prevalence globally and the leprosy trends started plateauing, deformities and complications continued to occur and dapsone resistance was documented[1]. Subsequently, from 1985 onwards, multidrug therapy (MDT) was the key public health intervention that helped in reducing the global leprosy burden substantially[1]. Initially, the duration of MDT was recommended as two years or until smear negativity for multibacillary (MB) leprosy. For paucibacillary (PB) leprosy, a two-drug combination of rifampicin and dapsone for six months and rifampicin once a month were recommended. Subsequently, over the years, based on the collective experience, the WHO through its two expert committees and a study group modified the treatment regimen. The key modifications were two years of fixed period for MB (1988) and later reduced duration for MB to 12 months (1998). Further, the WHO recommended single-dose regimen (rifampicin, ofloxacin and minocycline) for single-lesion PB patients[1]. During the implementation of MDT, national vertical programmes focussed on early case detection and treatment of all leprosy patients with MDT[2]. Most countries were successful in achieving leprosy elimination by the end of first decade of the current century, and vertical leprosy programmes were integrated into the primary health care services[3,4]. Such integration demanded further simplification of patient management practices including follow up. The WHO strategy for 2011-2015 focuses on sustaining the initiatives to reduce burden of leprosy in all the endemic communities[5].

A simplified approach to leprosy diagnosis and treatment is deemed important for the sustainability of leprosy control services under programmatic conditions. In this context, MB-MDT regimen given for six-month duration was proposed as uniform MDT (U-MDT) regimen for all types of leprosy. Ji and Saunderson[6] expressed concerns regarding this approach and the trial design not having a control group. These have been addressed in our earlier publication[7]. The goal of chemotherapy should be to shorten and optimize treatment regimen to achieve desired outcomes with minimum/acceptable side effects. For reducing the duration of MB-MDT, supportive evidence was available from experimental and clinical trials. Experimental studies suggested that MDT for 2-3 months was capable of killing almost all viable bacilli in the mouse footpad model[8,9]. Further, the rifampicin-resistant mutants in an untreated lepromatous patient were likely to be eliminated by three months' daily treatment with dapsone-clofazimine combination and by that time rifampicin with three monthly doses would have killed over 99.9 per cent of the viable *Mycobacterium leprae*[8]. This was further confirmed by a clinical trial, in which loss of infectivity of *M. leprae* after only one month of the WHO MB-MDT or with a single dose of rifampicin was documented[10]. It is, therefore, reasonable to believe that patients would respond to six months' MB-MDT, but a smaller number of them may relapse, who could continue on MDT without any risk of drug resistance. Second issue of importance is the addition of clofazimine for PB-MDT. Evidence from a randomized controlled clinical trial of PB-MDT plus daily clofazimine versus routine PB-MDT suggested that the proportion with persisting active skin patches was considerably lower in the clofazimine arm (7.5%) compared to PB-MDT arm (16%), and in the six month post-PB-MDT follow up, clofazimine group demonstrated better response than the control group (80 vs. 30%)[11]. Further, clofazimine could be potentially beneficial against type 2 reactions in leprosy patients[12]. In addition, the combination of three drugs may possibly reduce the chance of drug resistance. A controlled trial with control group could be justified only for a small fraction of highly bacteriologically positive patients (about 2% of newly diagnosed leprosy patients), who could be at risk of possible inadequate treatment and increased risk of relapse. However, based on the principle of equivalence, one would require a substantially large sample size for such a trial, which is practically not feasible. In view of the discontinuation of skin smears in the programmes[1], it will not be possible to identify such high-risk patients. U-MDT trial was undertaken as programme implementation research with phase IV clinical trial perspective. National Institute of Epidemiology (NIE) of the Indian Council of Medical Research (ICMR), in Chennai, India, coordinated the U-MDT trial. The primary objective of this trial was to assess treatment response to U-MDT in terms of relapse rate not exceeding a maximum cumulative level of five per cent at the end of five years. The secondary objectives were to assess acceptability, safety and compliance to the U-MDT regimen. Here, we present the final results of the trial.

Material & Methods

It was a single-arm open-field trial. The trial was initiated in October 2003 and the final five years'

follow up at the last site (Rohtas in Bihar, India) was completed in January 2014.

Sample size: Considering the five year maximum relapse rate of five per cent as acceptable limit (Poisson distribution; P_0=5%; P_a=3%) with the power of 90 per cent, type 1 error of 5 per cent (one-tailed test) and loss to follow up of 30 per cent in field situations, the required sample size was 2223 which was rounded off to 2500 for each type of leprosy.

Study settings: During 2003-2004, the trial was initiated at six sites - four districts in India (Pune, Kanpur, Tiruvannamalai and Villupuram) and two provinces in P. R. China (Guizhou and Yunnan). Two sites from India - Gaya and Rohtas districts were subsequently included in 2005 and 2007, respectively. The trial was conducted at the district level by leprosy control programme officers in three sites in India (Tiruvannamalai and Villupuram in Tamil Nadu and Pune in Maharashtra). At Kanpur in Uttar Pradesh, the trial was conducted by the National JALMA Institute for Leprosy and Other Mycobacterial Diseases (ICMR), Agra. In two sites of Bihar (Gaya and Rohtas), Damien Foundation India Trust, Chennai, conducted the trial in collaboration with the leprosy programme. In PR China, the trial was conducted as part of national leprosy control programme.

Study participants: Newly detected and treatment-naive leprosy patients were recruited in the trial. Patients with access to the clinic and available to receive U-MDT under supervision and willing for long-term follow up were included after obtaining written informed consent. Patients who had only neuritic manifestations or who had been previously treated for leprosy, were excluded.

Study drugs and treatment schedule: Study participants were given monthly-supervised doses of U-MDT in the presence of the investigators for six months. For adults, the regimen consisted of supervised pulse of 600 mg rifampicin, 300 mg clofazimine and 100 mg dapsone every four weeks along with daily-unsupervised course of 50 mg clofazimine and 100 mg dapsone. The supervised dosage for children aged 10-14 years was 450 mg rifampicin, 150 mg clofazimine and 50 mg dapsone every four weeks and 50 mg clofazimine every alternate day and 50 mg dapsone daily. For children <10 yr, the dose (mg) was adjusted to body weight (kg) as follows: rifampicin 10-20 mg/kg, clofazimine 1-2 mg/kg and dapsone 1-2 mg/kg of the body weight. All the drugs were supplied by the WHO with a special labelling of U-MDT for adult and child blister packs separately for the entire duration of the trial.

Data collection: The investigators of all the sites assessed every new leprosy patient for suitability for inclusion in the study as per the protocol. Patients who decided not to join the study or found ineligible were given regular MDT as per the national leprosy programme guidelines in India or P. R. China. During the treatment period patients were interviewed and carefully examined for adverse drug reactions (ADRs), leprosy reactions and neuritis at the time of their monthly visit for receiving the supervised dose of treatment. Subsequently, occurrence of clinical events such as relapse, reactions, disability and neuritis and other events such as migrations and deaths was recorded during the yearly follow up visits after completion of treatment. Patients developing new lesions, pain in the nerves, joint pains, fever and any other complaint were requested to report and were examined and treated as early as possible. The NIE, Chennai, monitored the trial for its duration and ensured adherence to the trial protocol at the trial sites. In addition, reporting forms were collected, scrutinized and entered in the trial database at NIE. Discrepancies found during scrutiny were clarified with the study sites. Further, quality checks were conducted through on-site supervision visits and periodic monitoring throughout the study period. Operational definitions used in the trial are given elsewhere[7].

The study protocol was approved by the Institutional Human Ethics Committees of the participating organizations. All the participants in the study provided written informed consent administered in their local languages. (Clinical Trials Registry of India: 2012/05/002696).

Data analysis: Baseline characteristics of the study participants at all the study sites were analyzed and frequencies were estimated. Per protocol analysis was done and person years (PY) for study participants were calculated from the time of completion of treatment to the observation of primary outcome (relapse) or from the time of recruitment till the time of lost to follow up due to suspected ADR (during treatment period) or non-clinical events or completion of five years post-treatment. Those with relapse, suspected ADR or any of the non-clinical events were right censored and thereafter they ceased to contribute to the person-time of observation. For those who had temporarily

migrated and then joined the study later, the maximum PYs contributed by them, *i.e.* from enrolment to each of those follow up time-points, were calculated. Event rates per 100 PY were also calculated. The rates were compared using Chi-square test. Further, cumulative risk [risk=1-$e^{(-\text{rate} \times \text{period})}$] of relapse for five years was computed. We used SPSS18.0 (SPSS Inc., Chicago, IL, USA) and OpenEpi[13] were used for data analysis.

Results

During October 2003 and June 2008, 3389 (98.6%) (PB=2091; MB=1298) of the 3437 new patients screened for the trial were enrolled (Fig. A, B). Forty eight patients could not be enrolled for various reasons including ineligibility (n=34), duplication of records (n=7), other reasons (n=6) and declined to participate (n=1). Of these ineligible patients,19 had pure neuritic leprosy and were put on routine MDT. Of the total recruited, MB% ranged between 27 per cent (168 of 631) in Gaya and 67 per cent (111 of 166) in P. R. China (Tiruvannamalai: 46% of 520; Villupuram: 45% of 505; Pune: 34% of 812; Kanpur: 40% of 316; Rohtas: 33% of 439). Of the total enrolled, 3169 completed the prescribed treatment. Thirty participants (PB=21 and MB=9) completed the treatment beyond nine months after initiation, and hence, they were excluded from subsequent analysis.

Findings among PB type of patients: Of the total 2091 PB patients enrolled,19 per cent (n=396) were younger than 15 years (mean age±SD of 29.3±15.1 yr) and 54 per cent (n= 1135) were male (Table I). Grade 2 disability (G2D) was present in three per cent (n=55) of them at recruitment, and nerve lesions were present in 33 per cent (n=691) of the patients. Evidence of mild reactions was found in one per cent (n=25) of the patients and 51 (2%) had neuritis at the time of enrolment.

Primary outcome: Two PB patients had clinically confirmed relapse (Table II). The relapse rate per 100 person years (PY) was 0.02 (total PY=8780) and the cumulative risk over five years was 0.11 per cent. One of the relapses occurred in the second year and the patient was put on routine MDT by the site investigator. The second relapse occurred in the third year (Table III) of follow up and was put on one more course of U-MDT. Both had their skin lesions 'improved' at the completion of the trial.

Secondary outcomes: Acceptance of the U-MDT regimen was 100 per cent for all the sites. Totally, 94 per cent completed U-MDT within nine months (52% within six months and rest in nine months). There were

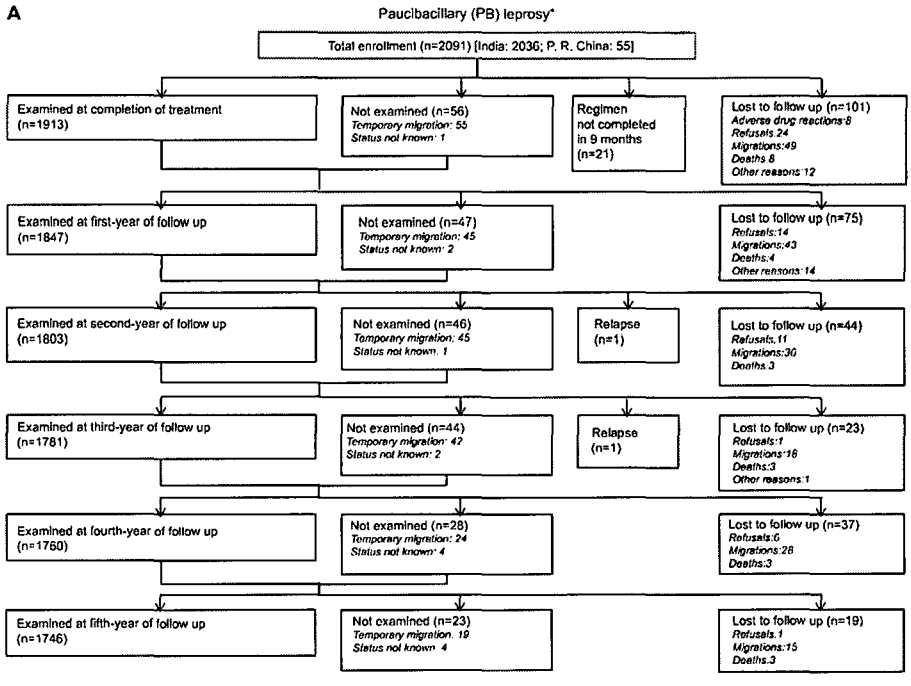

Fig. (A) Intake and follow up of paucibacillary leprosy patients from all the study sites, uniform multidrug therapy trial, 2003-2014. **Of the 3437 new leprosy patients screened for the trial, 48 (1.4%) were not enrolled due to various reasons [exclusion criteria=34; duplicates=7; other reasons=6; declined=1]. No details about PB/MB status of these 48 patients are available.*

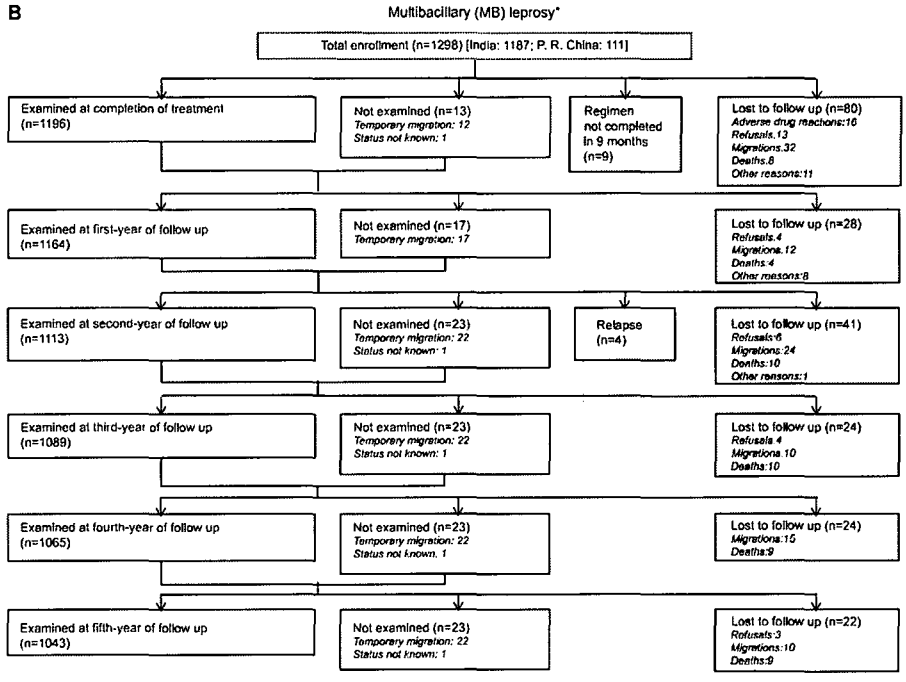

Fig. (B) Intake and follow up of multibacillary leprosy patients from all the study sites, uniform multidrug therapy trial, 2003-2014. **Of the 3437 new leprosy patients screened for the trial, 48 (1.4%) were not enrolled due to various reasons [exclusion criteria=34; duplicates=7; other reasons=6; declined=1]. No details about PB/MB status of these 48 patients are available.*

Table I. Baseline characteristics of study participants, uniform multidrug therapy trial, 2003-2014

Characteristics	PB (n=2091) n (%)	MB (n=1298) n (%)
Age group (yr)		
≤14	396 (19)	129 (10)
15-64	1652 (79)	1113 (86)
65+	43 (2)	56 (4)
Male gender	1135 (54)	853 (66)
Nerve lesions		
0	1400 (67)	486 (37)
1	452 (22)	227 (17)
2	146 (7)	242 (19)
≥3	93 (4)	343 (26)
Grade 2 disability	55 (3)	66 (5)
Mild reactions	25 (1)	49 (4)
Neuritis	51 (2)	61 (5)

MB, multibacillary; PB, paucibacillary

no complaints about clofazimine pigmentation. The investigators reported that skin pigmentation due to clofazimine was of short duration and acceptable to the enrolled patients with PB leprosy.

During the study period, a total of 645 special events were reported among PB patients. Of these, 301 events resulted in lost to follow up due to clinical (n=10) or non-clinical events (n=291). The remaining 344 were events that did not lead to lost to follow up (clinical events=114 and temporary migrations=230) (Table II).

At the end of five years post-treatment follow up, the death rate was 0.25 per 100 PY (n=24) among PB patients. Of these deaths, one was reportedly due to complications following leprosy reactions from Guizhou site in P. R. China. Seven deaths were due to injuries (suicide=2, snake bite=1 and motor vehicle accidents=4), followed by four cardiac problem-related deaths. Cause of death was unknown for four deaths.

Of the total PB patients recruited, 2.7 per cent (n=57) refused to continue in the study for various reasons. Majority of them were self-refusal for clinical examination during follow up (n=30). Twelve participants did not report any reason for discontinuation.

Among the lost to follow up, 27 were due to various reasons such as shifting outside the study area (n=20) and being found ineligible during the treatment

Table II. Rate of occurrence of clinical and non-clinical events* (per 100 person years) by type of leprosy, uniform multidrug therapy trial, 2003-2014

Type of events	PB		MB	
	n	Rate/100 person years	n	Rate/100 person years
Clinical events leading to lost to follow up				
Clinically confirmed relapse among new lesions	2	0.02	4	0.07
Suspected adverse drug reactions	8	0.79	16	2.64
Non-clinical events leading to lost to follow up				
Death	24	0.25	50	0.88
Migration†	183	1.94	103	1.81
Refusal	57	0.61	30	0.53
Others	27	0.29	20	0.35
Clinical events not leading to lost to follow up				
Neuritis	37	0.39	78	1.37
Type 1 reactions	51	0.54	114	2.01
Type 2 reactions	3	0.03	28	0.49
New lesions on account of reactions	23	0.24	76	1.34

*Multiple events were reported for each patient; †Refers to permanent migration leading to lost-to-follow up from the study; temporary migrations were 230 among PB and 117 among MB patients. MB, multibacillary; PB, paucibacillary

period (wrong diagnosis or pregnancy). P. R. China site removed four patients from the trial since they were either put on routine MDT by investigators (n=3) or as opted by the patient (n=1).

The clinical events leading to lost to follow up included eight suspected ADR (total PY=1009; rate=0.79). As per the WHO/TDR guidelines (*http://www.who.int/tdr/publications/documents/investigator.pdf?ua=1*) and based on available clinical notes, one of the ADR was classified as 'probably'(exfoliative dermatitis with jaundice) and seven as 'possibly' related to the drug. Of the reported clinical events, rate of occurrence (per 100 PY) of new lesions on account of reactions was 0.24 (n=23) and that of neuritis was 0.39 (n=37). Of the total neuritis, 24 were reported independently and 13 were reported along with type 1 reaction. Rate of occurrence of type 1 reaction was 0.54 (n=51). Type 2 reaction was 0.03 (n=3) per 100 PY from two PB patients (first year=2 and fourth year=1) who also had nerve lesions at the time of enrolment.

Status of skin lesions during follow up: Of the total PB patients, 97 per cent patients had either inactive or improved skin lesions at the time of completion of treatment and 0.5 per cent had static lesions at the end of fifth year of post-U-MDT (Table IV).

Findings among MB type of patients

Of the 1298 MB patients enrolled (mean age 35.3±16.1 yr), 10 per cent (n=129) were children younger than 15 years and 66 per cent (n=853) were male (Table I). G2D was present in five per cent (n=66) at recruitment and nerve lesions were present in 63 per cent (n=812) of the study participants. At enrolment, four per cent (n=49) had evidence of mild reactions and five per cent (n=61) had neuritis.

Primary outcome: Of the MB patients, four had clinically confirmed relapse (Table II) and the relapse rate was 0.07 per 100 PY (total PY=5379) and cumulative risk for five years was 0.37 per cent. Three relapses occurred during the second year and one in the first year. All of them were put on one more course of U-MDT. At the fifth year of post-treatment follow up, one patient from P. R. China had static skin lesions (Table III) and the rest had either 'inactive' (n=2) or improved (n=1) lesions.

Secondary outcomes: All of the MB patients accepted U-MDT regimen in all the sites. There were no complaints about clofazimine. The skin pigmentation due to clofazimine was reported to be of short duration and acceptable to the enrolled patients with MB leprosy. Of the total 1298 who accepted U-MDT, 94

Table III. Profile of the relapsed patients by type of leprosy, uniform multidrug therapy (U-MDT) trial, 2003-2014

Type of leprosy (study site)	Age (yr)	Gender	Time of occurrence of relapse	Clinical profile	Course of treatment	Status of skin lesion at completion of the study
MB						
Tiruvannamalai, India	41	Male	One year, eight months	Diagnosed and recovered from type 1 reaction during the first year post-U-MDT. Multiple, raised, combination of ill and well-defined, erythematous, new lesions	One more course of U-MDT	Inactive
Tiruvannamalai, India	37	Male	One year, seven months	Multiple, raised, combination of ill and well-defined, erythematous new lesions of two months duration	One more course of U-MDT	Improved
Villupuram, India	57	Male	One year; six months	A few erythematous well-defined smooth surface patches on face and both ear lobes. Great auricular nerve thickened on both sides	One more course of U-MDT	Inactive
P. R. China	38	Male	One year	Type 2 reactions. Many new skin lesions and oedemain hand. Had many nodules & erythema	One more course of U-MDT	Static*
PB						
Kanpur, India	34	Male	One year, nine months	New lesion, Type 1 reaction, neuritis	Routine MDT†	Improved
Tiruvannamalai, India	40	Female	Two years, six months	12 raised, combination of ill and well-defined, erythematous patches of various sizes in new sites (MB)	One more course of U-MDT	Improved

*Principal investigator communicated that the most recent skin smear examination of this patient was negative; †As preferred by the principal investigator. MB, multibacillary; PB, paucibacillary

per cent (n=1220) completed the regimen and 52 per cent (n=675) consumed doses within six months.

In all, 636 special events were reported among MB patients. Of these, 223 were clinical (n=20) or non-clinical (n=203) leading to lost to follow up. The remaining 413 events (clinical=296 and temporary migrations=117) did not result in lost to follow up (Table II). Fifty MB patients died during the follow up period (rate: 0.88 per 100 PY). Of these, nine each were due to respiratory failure and liver diseases and eight deaths were due to cardiac problems. Seven deaths were reportedly due to injuries (suicide=4; drowning=2; homicide=1). Ten MB patients died due to various causes. Cause of death was unknown for seven patients.

Of the 30 patients who refused to continue in the study for various reasons, 12 patients refused clinical examination during follow up, and for five of them, the regimen was changed and nine did not report any reason for discontinuation. Three patients refused because they were not interested in continuing in the study and one patient refused on account of stigma.

Among the lost to follow up reported under 'others' events, 20 were due to various reasons such as shifting

Table IV. Clinical status of skin lesions at the completion and post-treatment by type of leprosy, uniform multidrug therapy trial, 2003-2014

Clinical status	PB, n (%)				MB, n (%)			
	Lesion inactive	Improved	Static	Total	Lesion inactive	Improved	Static	Total
At the completion of treatment	803 (42.0)	1060 (55.4)	50 (2.6)	1913	125 (10.4)	1016 (84.9)	56 (4.7)	1197*
First year post-treatment	1229 (66.5)	597 (32.3)	21 (1.1)	1847	474 (40.7)	669 (57.5)	21 (1.8)	1164
Second year post-treatment	1443 (80.0)	343 (19.0)	17 (0.9)	1803	642 (57.7)	464 (41.7)	7 (0.6)	1113
Third year post-treatment	1562 (87.7)	215 (12.1)	4 (0.2)	1781	788 (72.4)	292 (26.8)	9 (0.8)	1089
Fourth year post-treatment	1585 (90.0)	173 (9.8)	3 (0.2)	1761†	836 (78.5)	223 (20.9)	6 (0.6)	1065
Fifth year post-treatment	1594 (91.2)	146 (8.4)	8 (0.5)	1748‡	842 (80.7)	190 (18.2)	11 (1.1)	1043

*One patient (MB) refused during treatment from Gaya site was examined and the clinical status of skin lesion was static in the first year; †One patient (PB) who discontinued - refusal during first year from Gaya site was examined and the clinical status of skin lesion was cured in the fourth year; ‡Two patients (PB) who discontinued - refusal during first year and fourth year, respectively, from Gaya site were examined and the clinical status of skin lesions were cured in the fifth year. MB, multibacillary; PB, paucibacillary

outside the study area (n=13). P. R. China site removed seven patients from the trial since five of them were put on routine MDT [either by the investigators (n=4) or as opted by patient (n=1)] and two patients received additional dose of clofazimine.

Of the clinical events leading to lost to follow up, 16 were due to suspected ADRs (total PY=605; rate=2.64 per 100 PY). Of these, seven had dapsone-induced exfoliative dermatitis and were classified as 'probably' and rest as 'possibly' related to the drug. Of the reported clinical events, rate of occurrence (per 100 PY) of new lesions on account of reactions was 1.34 (n=74) and that of neuritis was 1.37 (n=78). Of the neuritis, 43 were reported independently and 29 were reported along with type 1 and six with type 2 reactions. Rate of occurrence of type 1 reaction was 2.01 (n=114) and that of type 2 reaction was 0.49 (n=28) per 100 PY (Table II). Type 2 reactions (28 events from 24 patients) occurred during treatment and throughout the follow up.

Status of skin lesions during follow up: Proportion of MB patients with inactive and improved skin lesions was 95 per cent at the end of the completion of treatment. Static lesions were present in 1.1 per cent at the end of fifth year of post-U-MDT (Table IV).

Discussion

Our observation of low level of relapse was consistent with the findings from the most recent randomized controlled trial from Brazil that compared U-MDT with regular MDT (0.09 per 100 PY; two relapses during 2139 PY)[14,15]. Rate documented in our trial was much lower than the reported relapse rates from programmatic settings and other field trials[16-21] [maximum rates (per 100 PY): 0.65 in PB and 2.04 in MB]. Based on information available from leprosy programmes, the WHO reports frequency of relapse per year as 0.1 per cent for PB and 0.06 per cent for MB[22]. According to India's leprosy programme, the country as a whole reported 433 clinical relapses for the year 2013-2014 with one larger province reporting the maximum (n=236)[21].

In the present study, almost all the new patients in the eight centres (98.6%) were enrolled and 94 per cent of them completed U-MDT treatment in nine months indicating good acceptability and compliance. The profile of study participants represented the actual scenario of new leprosy cases at the community level. Among these patients, low relapse rates were observed after completion of U-MDT. Thus, in this trial, apart from the question of extent of relapses in PB and MB patients, it was possible to consider overall effectiveness of this treatment regimen under routine programmatic conditions. Since this study was taken up for patient treatment, case detection became more proactive from the point of view of recruitment. This would explain a lower level of MB proportion among the new cases in this study.

With regard to safety of the regimen, the addition of clofazimine could potentially offer clinical and cost benefits. In terms of clinical benefits, clofazimine possibly reduces incidence of neuritis in PB and type 2 reactions in MB. The present study was not designed to test these beneficial effects. However, the observed incidence rates of neuritis and type 2 reactions and cumulative risk of neuritis (1.94% and 6.63% in PB

and MB, respectively) and type 2 reactions (0.16% and 2.43% in PB and MB, respectively) were lower than those reported in the literature. For instance, the overall incidence of neuritis reported ranges between 6.1 and 34 per cent[23-29]. Similarly, reported rates (range) of type 2 reactions are higher in hospital-based studies (overall: 2-28.9%) than in the field leprosy programmes (overall: 0.2-4.6%; MB: 1-8.9%)[23-27,30-34]. India's national leprosy programme reported 12,901 episodes of reactions/neuritis episodes for 2013-2014 for the entire country[18]. In the programmatic context, addition of clofazimine may theoretically add to the cost to treat leprosy. However, such costs will be offset by reduction in morbidity among PB patients and hence reduced cost of management of such morbidities. Reduced duration of regimen for MB will further halve the cost of regimen. Thus U-MDT regimen will actually reduce the cost of leprosy treatment.

Advantages and implications for leprosy programmes

U-MDT trial was essentially a programmatic implementation research. Hence, it is worth considering the findings in the context of its implications for programmes. Nearly all new treatment naive patients from the study areas were included. Proportion of MB was lower than PB (38 vs. 62%) and MB patients had nerve involvement. We expect this to be generally representative of the real-life situation in the programme. We tried to keep implementation of the U-MDT as per the programme routine. However, the case detection had been proactive and the follow up of the patients was more rigorous. It is expected that if U-MDT is implemented in the programme situation with appropriate sensitization of patients and providers, it will help in effectively reducing leprosy prevalence at the district/regional levels as well.

In the national leprosy programme (India), skin smear and skin biopsies are not performed. In the absence of such testing, it is essential to consider how much could be the probable misclassification in the present study. PB-MB grouping is employed primarily on the assumption that the protective immunity is inversely correlated with the number of lesions[35]. In programmatic conditions, it was thus possible that some of the leprosy patients would have been misclassified as PB or MB[36]. However, the extent of such misclassification in the present study seems to be minimal. For instance, a low rate of type 2 reactions among PB (rate=0.03; risk=0.16%) was observed as compared to 0.49 per 100 PY among MB patients (risk=2.43%, $P<0.001$).

Two study sites carried out skin smear test as part of their implementing agency's or country's policy and practice although skin smear examination was not required as per common protocol. P. R. China sites performed skin smear examination and documented rapid fall in bacteriological index with almost 95 per cent MB patients becoming smear negative at the end of five years of follow up[37,38]. This information further supports the applicability of U-MDT in the programme.

Finally, there is a need to consider implications of trial findings on the follow up strategy while adopting U-MDT in programmes. All the suspected ADRs were reported within a maximum of three months, and all the relapses occurred within first three years after treatment completion. Further, it was noted that the occurrence of type 2 reactions was continuing during post-treatment follow up. Hence, the primary health care physicians will require necessary clinical expertise to recognize and manage such clinical events. There is a need to educate and counsel patients to be alert about any such event and report immediately to the primary health care providers.

Only a small number of patients in PB and MB had static lesions at the end of five years post-U-MDT. Since relapses occurred within first three years after U-MDT, a carefully crafted strategy for periodic follow up algorithm during the first three years after MDT might help in picking up relapse patients relatively early. In 2013-2014, India's leprosy programme confirmed that a sizeable number of suspected relapses at the primary health care level (n=486) were referred and confirmed at the district hospital level (n=433)[21]. Hence, the national leprosy programmes could implement such a strategy of identification, referral and management at appropriate levels.

Limitations and biases

Our study had few limitations and biases. Key limitation was that of inability to meet the sample size requirements for MB. Due to overall reduction in prevalence, adequate number of patients could not be enrolled in the given geographic areas of the study sites. Further, the sample size was calculated for an expected relapse rate of three per cent (P_a) in the study groups, *i.e.*, two per cent less than an assumed level of five per cent (P_o). At the end of the trial, we observed relapse of <1 per cent. The power to detect this two per cent difference (*i.e.*, between 3 and 1%) was 100 per cent for PB and 99.9 per cent for MB group. Therefore, even with the recruited number of

participants, we had closer to 100 per cent power to support our conclusions of efficacy of the six-month U-MDT regimen to prevent relapses in PB and MB types of leprosy patients.

In terms of biases, two types of selection biases might be considered. The study sites were purposively selected on the basis of ability to recruit patients and to offer better services and follow up. Further, as only those patients who were willing, were enrolled, there could be some level of selection bias at the level of participants. However, in most of our field sites, almost all the patients opted for U-MDT, and hence, such selection bias would be minimal. Further, due to the active nature of follow up from the investigators and the coordinating centre, it is possible that research bias might have contributed to the higher treatment completion rates than the reported figures in programme settings.

On the basis of our findings, it is concluded that the observed low relapse among the newly detected PB and MB leprosy patients from India and P. R. China demonstrates efficacy and effectiveness of U-MDT regimen in both PB and MB patients. The regimen was found to be acceptable and safe for both the groups of patients. The negligible proportion of static lesions in the MB patients of our trial documented the effectiveness of shortened duration of regimen. Treating physicians need to be aware as well as vigilant about monitoring leprosy patients for special events during and after completion of MDT for about three years. Based on such monitoring and assessments, treating physicians can decide to prolong treatment duration for individual patients. The global and national programmes should consider the evidence for programmatic adaptation of U-MDT strategy for all types of leprosy patients.

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***Conflicts of Interest*:** None.

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International open trial of uniform multi-drug therapy regimen for 6 months for all types of leprosy patients: rationale, design and preliminary results

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Summary

OBJECTIVE To describe the rationale, design and preliminary results of an open trial of 6 months uniform multi-drug therapy (U-MDT) for all types of leprosy patients assuming a cumulative relapse rate not exceeding 5% over 5 years of follow-up.

METHODS We intended to recruit 2500 patients each in multi-bacillary (MB) and pauci-bacillary (PB) groups from India (five centres) and China (two centres). Standardized clinical criteria were used to assess skin lesions in the field.

RESULTS A total of 2912 patients enrolled from November 2003 to May 2007 (India, 2746; China, 166). MB patients constituted 39% and 3% had grade 2 disability. During follow-up, 27 patients (0.9%) developed new lesions. Of these, 78% were on account of reactions. Six patients had clinically confirmed relapse. Clofazimine-related skin pigmentation was short-lived and was acceptable to patients. We analysed data for clinical status of skin lesions. About 2.9% of patients were lost to follow-up; 85.9% completed treatment, of whom 19% had inactive skin lesions. PB patients responded better than MB patients (27% *vs.* 6%; $P < 0.001$). At the end of the first ($n = 2013$) and second year ($n = 807$) of follow-up post-U-MDT, in 49% and 46% patients, lesions were inactive, respectively (59% and 57% in PB, 37% and 28% in MB; $P < 0.001$).

CONCLUSION U-MDT appears to be promising with respect to clinical status of skin lesions.

keywords leprosy chemotherapy trial, clinical trial, uniform multi-drug therapy

Introduction

Prevalence of leprosy decreased globally, clearing the way for integrating leprosy services into the general health services (WHO 2000). In this context, the World Health Organization (WHO) and the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) are supporting a multi-centric trial to assess efficacy of a 6-month uniform multi-drug therapy (U-MDT) for all types of leprosy patients. The National Institute of Epidemiology (NIE) of the Indian Council of Medical Research, India, is coordinating the trial, whose primary objective is to assess the efficacy of U-MDT under programme conditions for all types of leprosy patients. Main outcome measure is cumulative level of relapse rate not exceeding 5% after 5 years. Here, we describe the study's rationale, design and preliminary findings.

Rationale

At the end of the year 2000, the global prevalence of leprosy dropped below 1 per 10 000 inhabitants (WHO 2002a). WHO policy is to sustain multi-drug therapy (MDT) coverage and to encourage general health services to take on the responsibility of leprosy case detection and

management facilities (World Health Organization 2000, 2005). Currently there is an urgent need to involve the general health services for detecting and managing leprosy patients to sustain leprosy control. To fulfil this challenge, a further simplified MDT, effective under programme conditions, could prove to be the key. Accumulated scientific data over the past three decades demonstrate that such a possibility exists (World Health Organization 2002b).

Leprosy patients present mostly with skin patches and some with disabilities. Patients are encouraged to report for examination and treatment. WHO supplies high-quality MDT free of cost, and now is the time to make treatment more patient-friendly and easy to administer by the general health services. Patients suffering from any disease expect facilities for diagnosis and treatment to be available to them as close to their homes as possible. As a matter of principle, leprosy patients should be treated like any other patients. This should become possible when leprosy services become integrated within the general health services. Treatment has to be safe, efficacious, simple to follow, and provided to patients in a way that respects their human dignity. This treatment should be as short and cost-effective as possible.

In keeping with these principles, it was possible to propose a common or U-MDT for all leprosy patients, which is essentially the 6-month MDT for multi-bacillary leprosy (MB) consisting of clofazimine, dapsone and rifampicin. MB–MDT has been used for several years worldwide, and we have adequate information on its efficacy. However, in the context of U-MDT implementation, two issues need to be elucidated: One is reducing the duration of treatment for MB patients from 12 months. Evidence from experimental studies suggests that 2–3 months' MDT is capable of killing almost all viable bacilli in the mouse footpad model (Ji *et al.* 1996a; Banerjee *et al.* 1997). An experimental study further suggests that the rifampicin-resistant mutants in an untreated lepromatous patient are likely to be eliminated by 3 months' daily treatment with dapsone–clofazimine combination and by that time rifampicin with three monthly doses would have killed over 99.999% of the viable *Mycobacterium leprae* (Ji *et al.* 1996a). This has been further confirmed by a clinical trial in which loss of infectivity of *M. leprae* after only 1 month of WHO MB–MDT or with a single dose of rifampicin was documented (Ji *et al.* 1996b). It thus appears that a large number of MB patients get longer treatment than necessary and a negligible fraction of MB patients would perhaps need treatment longer than 6 months. All patients are expected to respond to 6 months' MB–MDT, but a small number may relapse. Relapsed patients could easily be retreated with the same MDT, since there is virtually no risk of drug-resistant mutants emerging. It is logical to expect better compliance from the patients if treatment were reduced by 6 months.

The second important issue is the addition of clofazimine for pauci-bacillary (PB) patients. In a randomized controlled clinical trial conducted in India, efficacy of PB–MDT plus daily clofazimine was compared with PB–MDT (Katoch *et al.* 1999). The proportion with persisting active skin patches was considerably reduced by addition of clofazimine (16% in the PB–MDT arm *vs.* 7.5% in the PB–MDT plus daily clofazimine arm) at the end of 6 months' treatment. In the next 6 months of follow-up, activity fell by 80% in the study group compared with only 30% in the control group. Clofazimine was well accepted by patients, pigmentation was minimal and rapidly disappeared after stopping treatment.

Side effects and toxicity for the three drugs in MB–MDT are generally rare and widely known. However, there is almost no data from prospective studies on the side effects of MDT. Therefore, all types of leprosy patients can be provided with U-MDT and was thus considered safe to initiate this regimen under programme conditions.

Methods

Study design

An open field trial with emphasis on close monitoring of patients during treatment and for at least 5 years after completion of U-MDT was proposed. In choosing this design, the Technical Advisory Group (TAG) for elimination of leprosy at WHO concluded that sufficient scientific evidence was available for recommending implementation of U-MDT under programme conditions with adequate safeguards (World Health Organization 2002a). The group recommended close monitoring to ensure adequate care to the patients (World Health Organization 2002a).

Globally, the proportion of MB or PB patients among newly detected cases varies substantially. PB leprosy patients constitute the substantial majority of cases and for them the questions of interest concern adding clofazimine, its acceptability and whether it could be tackled in an open study design. The proportion of MB patients among newly detected cases varies substantially from country to country (27–91%) (WHO 2007). In India, it comprises around 45% (World Health Organization 2007) and varies from state to state. For the districts where U-MDT could be implemented, the reported MB portion is 30%. Further, a study conducted in North India (van Brakel *et al.* 2005) indicates that 50% of MB patients are smear negative borderline-tuberculoid patients. With respect to MB patients, there is a risk of inadequate treatment for highly

bacteriologically positive patients, who comprise about 2% of newly diagnosed leprosy patients. Even in this group it is not certain whether the reported high relapse rates (WHO 2003) are on account of relapse or re-infection. In the event of relapse, patients could easily be managed by administering an additional course of U-MDT. A randomized controlled trial could be justified only in this small fraction of highly bacteriologically positive patients. It would need a control group of patients receiving 12 months MB–MDT. Based on the principle of equivalence, the required number of patients for the study would be very large. These patients would be widely scattered in vast geographical areas and the trial would need extremely large inputs. Such a trial is not a practical proposition. Further, the practice of taking skin smears was discontinued in leprosy control programmes years ago (World Health Organization 1998). Hence, it may not be possible even to identify patients who possibly could be at higher risk for relapses. Such a trial would have a time span of several years and might not be useful to answer the immediate questions for simplified U-MDT through general health services. In view of existing strong scientific knowledge and the practical constraints, programme implementation is adopted rather than the conventional randomized controlled trial with blinding. However, the design has a phase IV clinical trial perspective.

Sample size

The sample size was calculated on the basis of Poisson distribution, since the primary outcome measure (relapse) is expected to have very low frequency (Shiue & Bain 1982). There is no consistent information on relapses in MB patients. Some studies report relapse rates as high as 4% or more and others show the risk to be negligible even in cases with high initial bacteriological index (Becx-Bleumink 1992; Jamet & Ji 1995; Chen *et al.* 1999; Gebre *et al.* 2000; Girdhar *et al.* 2000; Shaw *et al.* 2000; Ganapati *et al.* 2001; Lockwood 2004). Based on a survey from 28 leprosy control programmes, WHO estimated that the annual relapse rate was 0.77% for MB and 1.1% for PB patients (WHO 1995). There are no clear answers to this complex question but re-infection could be an explanation. Relapse is the parameter that could be considered as an outcome measure in field practice. Since new lesions occur on account of both disease activity and reactions, the specificity of new lesions as markers of relapse will remain doubtful. In a review article, expected cumulative probability for relapses in PB leprosy following WHO–MDT is estimated as approaching 5% over 10 years duration (Ponnighaus & Sterne 1995). Since in several of the published studies, information on leprosy is obtained through routinely collected data from programme conditions, the estimates of relapse may not be realistic. Regularity of treatment details might not have been carefully considered before working out the relapse rates. We therefore, considered a 5-year maximum cumulative relapse rate of 5% that would satisfy the patients' interest. Hence, P_0 would be 5% and P_a was assumed to be 3%. We further adopted a one-tailed test approach. Based on a type I error of 5% and power of 90%, the calculated sample size was 1713. To compensate for a presumptive loss during 5-year follow-up, we inflated the sample size by 30% to 2223 and rounded it off to 2500 leprosy patients. Since the analysis is planned for MB and PB patients separately, the same sample size is applicable for each of the two types.

Ethical considerations

The scientific and ethics committees of NIE approved the proposal for technical and ethical issues, respectively. The screening committee of the Health Ministry of the Government of India examined and approved the protocol in February 2003. Experts from TAG and the ethical review committee of WHO intensively discussed the U-MDT study. WHO approved the proposal in February 2003 (WHO 2002c). The informed consent form explained treatment options currently available, how U-MDT differs from existing regimens, risks, benefits and an alternative to participation.

Participants

All newly detected and treatment-naive leprosy patients were eligible for the trial. We excluded patients if they had only neuritic manifestations, had prior treatment for leprosy, were returned defaulters or relapsed patients. Pure neuritic patients were not recruited for two reasons: it would be difficult to assess the outcome in these patients, and diagnosis of pure neuritic leprosy is confined to India although case reports are available from other countries such as Brazil (Jardim *et al.* 2004). Patients with easy access to the clinic and eligible to receive U-MDT under supervision and for long-term follow-up were considered. Participants were included in the study after receiving their informed consent.

Study sites

We included centres with history of high incidence of leprosy of about 300 patients per year. Initially, we included six centres in the trial – four in India (Tiruvannamalai, Villupuram, Pune and Kanpur) and two in China (Guizhou and Yunnan). The number of new cases detected

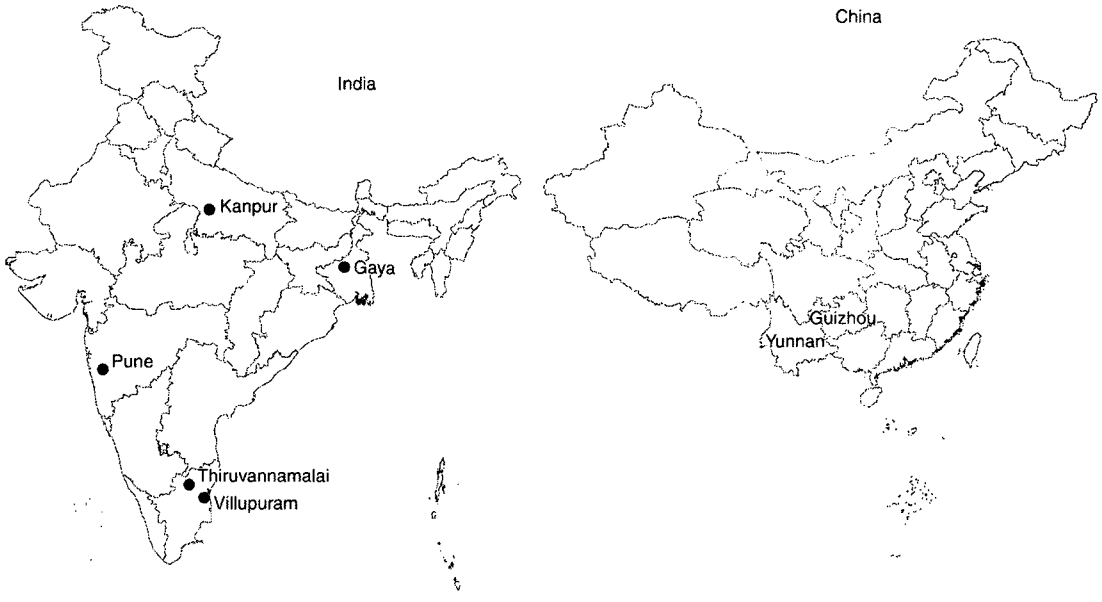

Figure 1 Location of centres participating in U-MDT trial.

in 2001–2002 ranged from 200 (China) to 3400 (Villupuram, India) in these centres. Gaya district of India was included in 2005 (Figure 1). In three centres in India (Tiruvannamalai and Villupuram in Tamil Nadu and Pune in Maharashtra), district level managers and their staff carry out the activities; in Kanpur in Uttar Pradesh, the trial is conducted by the National JALMA Institute of Leprosy and Other Mycobacterial Diseases and in Gaya in Bihar the Damien Foundation India Trust (DFIT) is responsible. In China, the trial is conducted as part of national leprosy control programme.

Procedures

The Principal Investigator (PI) of each trial centre assessed every new patient for suitability for inclusion in the study according to the protocol. Patients who decided not to join the study were given standard WHO–PB or MB–MDT. NIE conducted standardization workshop on data collection and transmission for all PIs in September 2003. PIs conducted standardization training for their centre staff. All data were recorded on standardized, colour-coded forms. Centres transmitted the hard copy of the filled in reporting forms to NIE monthly.

A case of leprosy was defined as a person having hypopigmented or reddish skin lesion(s) with definite loss of sensation with or without involvement of the peripheral nerves – as demonstrated by definite thickening with loss of sensation – who was yet to receive a full course of treatment. Sensation was measured according to standard clinical examination procedures of leprosy control programmes in field settings, using feather/paper and pin. We further classified patients on the basis of skin patches as either PB (up to five patches) or MB patients (more than five patches). Patients were assessed for disability using WHO disability grading as follows: (1) no loss of sensation or visible deformity or damage (grade 0); (2) loss of sensation without visible deformity or damage (grade 1); presence of visible deformity or damage (grade 2).

Patients included in the trial are given the monthly-supervised dose of 6-month U-MDT in the presence of the PI or his/her nominee. For adults, the regimen consists of a supervised pulse of 600 mg rifampicin and 300 mg clofazimine every 4 weeks along with a daily, unsupervised course of 50 mg clofazimine and 100 mg dapsone. For children aged 10–14 years, the regimen comprises 450 mg rifampicin and 150 mg clofazimine every 4 weeks, 50 mg clofazimine once every other day and 50 mg dapsone daily. For children younger than 10 years, the dose (mg) is adjusted to body weight (kg) as follows: rifampicin 10–20, clofazimine 1–2 and dapsone 1–2 mg/kg of the body weight. At each clinic visit for the supervised dose of treatment, patients are interviewed and carefully examined for side effects, reactions and neuritis. Drug administration is stopped or temporarily suspended at the discretion of the PI, in the following situations: (i) occurrence of severe intercurrent illness; (ii) adverse drug reactions; (iii) patient's refusal to continue treatment; (iv) severe

complications requiring cessation of treatment; (v) any other reason considered justified by the PI. If a patient fails to attend a monthly clinic, he/she is contacted within 24 h, to find out why. Patients who complete the regimen within 9 months are considered regular patients; those who do not complete the prescribed number of doses in 9 months are considered irregular, are removed from the study and are offered regular MDT.

PIs assess patients' clinical progress based on standardized clinical criteria. We defined a patient as 'lesion inactive' when the patient met the following criteria: (i) total disappearance of all lesions or reduction of size in all lesions with only residual or decreased hypo-pigmentation; (ii) absence of infiltration and erythema in all lesions; (iii) partial or total recovery of sensation in all lesions. Patients meeting any or all the following criteria are termed as 'improved': (i) reduction of size in some lesions; (ii) absence of infiltration and erythema in some lesions; (iii) recovery of sensation in some lesions. Patients with any or all of the following criteria are termed as 'static': (i) no change of size in any lesion; (ii) persisting infiltration and erythema in all lesions; (iii) no recovery of sensation in any lesion. Deterioration was defined as appearance of new skin lesions in patients with improved/static skin lesions.

Patients are followed up for occurrence of special events such as relapse, reactions, neuritis and adverse drug effects annually after completion of treatment. Patients developing new lesions, pain in the nerves, joint paints, fever, etc. are requested to report to the respective treatment sites as early as possible. We clinically defined relapse as development of one or more new skin patches consistent with leprosy without evidence of reactions in a patient after completion of six doses of U-MDT and after the earlier lesions became inactive. The PIs were experienced in distinguishing relapses from reactions. However, differentiating relapses and reactions under programme conditions is still difficult and clinicians tend to err on the relapse side in the best interest of the patients. Reactions were classified as type 1 and 2 reactions. Type 1 reactions were defined as occurrence of any of the following manifestations: (i) existing skin lesions becoming reddish and swollen; (ii) painful, tender and swollen peripheral nerves, including signs of nerve damage such as loss of sensation and muscle weakness; (iii) with our without constitutional symptoms such as fever and malaise. Type 2 reactions were defined as occurrence of short-lived and recurrent crops of tender reddish subcutaneous nodules that may ulcerate with signs of systemic involvement with fever, and inflammation in lymph nodes, nerves, eyes, joints, testes, fingers, toes or other organs. Neuritis is defined as appearance of definite new areas of loss of sensation and/or new muscle weakness with or without accompanied tenderness or pain in the affected nerves. Patients are encouraged to report these events voluntarily during and after 5 years. We followed WHO guidelines for management of reactions, neuritis and adverse drug effects (WHO 1998).

Data analysis

Enrolment began from November 2003 to November 2005 in all centres, except Gaya, India where the trial was initiated July 2005. We undertook interim analysis of available data until 1 May 2007, analysing baseline characteristics and special events reported from all centres. Clinical status of skin lesions was analysed at the completion of treatment and at the end of first/second year of follow-up for all centres. We expect all participating centres to complete follow-up by 2013 and final results will be available by 2014.

Interim results

Enrolment status

From November 2003 to May 2007, the trial enrolled 2912 patients including 166 from China (Table 1). Information on patients who opted for routine MDT was incomplete. It was available from only one centre and only in the initial stages of the study. Generally, all patients opted for and accepted U-MDT in all centers.

Characteristics of patients enrolled

Fourteen percent (n = 422) of the 2912 patients were children younger than 15 years (Table 2). 59% were males. MB patients constituted 39% of the patients and

Table 1 Enrolment status by type of leprosy patients, uniform multi-drug therapy (U-MDT) trial, November 2003 to May 2007†

	Patients enrolled		
Centres	PB	MB	Total
India			
Tiruvannamalai	281	237	518
Villupuram	277	228	505
Pune	537	284	821
Kanpur	194	128	322
Gaya‡	432	148	580
China			
Guizhou	44	86	130
Yunnan	12	24	36
Total	1777	1135	2912

†As of May 2007.
‡Trial started in July 2005.

Table 2 Baseline characteristics (% in parentheses) of 2912 patients enrolled for uniform multi-drug therapy (U-MDT) trial, May 2007

Characteristic	PB	MB	Total
Number of patients	1777 (61)	1135 (39)	2912 (100)
Age group			
≤14	319 (76)	103 (24)	422 (14)
15–64	1414 (59)	976 (41)	2390 (82)
65+	44 (44)	56 (56)	100 (3)
Male gender	968 (56)	747 (44)	1715 (59)
Nerve lesions			
0	1222 (73)	457 (27)	1679 (58)
1	345 (63)	206 (37)	551 (19)
2	125 (38)	207 (62)	332 (11)
≥3	85 (24)	265 (76)	350 (12)
Disability (WHO grade 2)	45 (46)	53 (54)	98 (3)
Mild reactions	17 (35)	32 (65)	49 (2)
Neuritis	26 (37)	45 (63)	71 (2)

3% (n = 98) had grade 2 disability. Nerve lesions were present in 42% (n = 1233). Of these, 350 had three or more nerve lesions. Evidence of mild reaction was found in 49 patients and 71 patients had neuritis at enrolment.

Special events

We analysed special events reported from all the centres as of May 2007. Clofazimine-related pigmentation of the skin was usually short-lived and acceptable to patients. From November 2003 to May 2007, we observed a total of 218 special events (India, 153; China, 65) in 174 patients (Table 3). Of these, 145 occurred in MB patients and 73 in PB patients. Fifty-three percent of these events (115/218) occurred during the treatment phase. Eighty-four patients were lost to follow-up (48 during treatment; 16 during the first year, 10 each during the second and third year post-treatment follow-up).

Table 3 Special events (n = 218) reported by 174 patients by type of leprosy during uniform multi-drug therapy (U-MDT) trial, May 2007

Special events	PB	MB	Overall
New lesions on account of reactions	3	18	21
Clinically confirmed relapse	2	4	6
Reactions			
Type 1	3	35	38
Type 2	3	14	17
Neuritis	11	28	39
Adverse drug reaction	3	10	13
Discontinuation from the study			
Refusals	9	5	14
Migrations	26	20	46
Deaths	10	11	21
Others	3	0	3
Total	73	145	218

Twenty-seven patients developed new lesions. Of these, 11 developed new lesions during treatment and the remaining 16 during follow-up. Of these 27 patients, 21 developed new lesions on account of reactions. Six patients were clinically compatible with relapse. Three of these relapses occurred in the first year, two were reported during the second year and one patient developed relapse in the third year of follow-up. All these patients were assessed as 'lesion inactive' at the completion of treatment. Subsequently they developed new lesions, and were given another course of U-MDT, and are being followed up.

Of the 84 patients who discontinued, 14 refused treatment. Of these 14 patients, 10 did so for reasons not stated. Two patients refused treatment. One patient with a regressed single patch did not believe that the patch was due to leprosy and another patient whose patches regressed after two doses believed that he was cured and did not require more therapy. Three patients discontinued treatment for 'other' reasons: pregnancy; unspecified reasons and irregular treatment attendance. A total of 46 patients were lost to follow-up on account of migration, 20 of these during the treatment phase.

There were 55 reaction episodes (38 type 1 and 17 type 2 reactions). Of these, 23 occurred during the treatment phase, the remaining 29 occurred afterwards. Thirty-nine neuritis events were reported, of which 16 occurred along with reactions. Eleven patients reported neuritis during the treatment phase, 13 patients reported adverse drug reactions. Of these 13 events, 11 were due to dapsone (seven had exfoliative dermatitis and four had non-specific dermatitis). One patient reported hepatitis whose cause was not known. One patient developed mononucleosis.

All 21 reported deaths were due to causes other than leprosy and were unrelated to U-MDT. Four deaths were attributed to hepatitis. Two deaths each were due to unknown cause, ischaemic heart disease and senility; one each was due to suicide, alcoholism, accident, cardiac arrest, chronic fever, duodenal ulcer, diarrhoea, typhoid, renal failure, respiratory failure and perforation of peptic ulcer.

Assessment of clinical status of skin lesions

Of the 2912 patients, 48 were lost to follow-up as of May 2007 (Figure 2). Of those remaining, 2503 patients (86%) completed treatment. About 99% (n = 2480) of patients completed treatment within the stipulated period. Of these, 19% were assessed as 'lesion inactive', 78% as 'improved', 3% as static and 0.2% as deteriorated at completion of

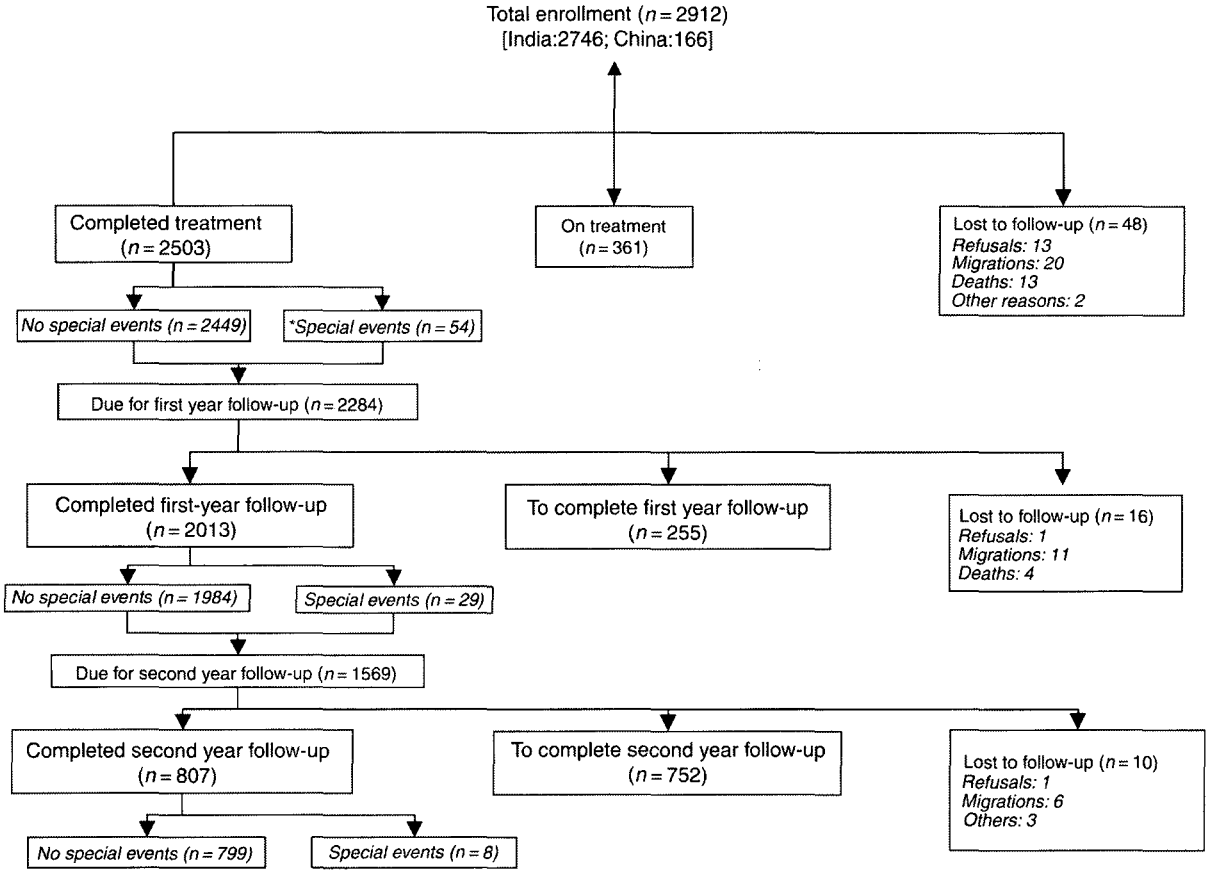

Figure 2 Uniform multi-drug therapy (U-MDT) regimen for 6 months for all types of leprosy patients, profile of the trial, May 2007.

Table 4 Clinical status of skin lesions by type of leprosy at the completion of treatment and first and second year of post-uniform multi-drug therapy (U-MDT) treatment, May 2007

	PB					MB				
Clinical status	Improved	Lesion inactive	Static	Deteriorated	Total	Improved	Lesion inactive	Static	Deteriorated	Total
At the completion of treatment	1049 (70)	408 (27)	37 (3)	1 (0.1)	1495	897 (89)	64 (6)	44 (4)	3 (0.3)	1008
First year post-treatment	491 (41)	702 (59)	5 (0.4)	0 (–)	1198	505 (62)	302 (37)	7 (1)	1 (0.1)	815
Second year post-treatment	212 (42)	290 (57)	3 (1)	0 (–)	505	216 (71)	83 (28)	3 (1)	0 (–)	302

Values are given as *n* (%).

treatment (Table 4). The proportion with inactive lesions among PB patients was greater than among MB patients (27% *vs.* 6%) (χ^2 = 177; $P < 0.001$) in this group.

A total of 2284 patients were due for first year follow-up; 16 were lost and 2013 (88%) patients completed first year follow-up. Of these, 1004 (49%) were classified as 'lesion inactive', 996 (49%) as 'improved' and 0.6% as 'static'. Amongst those who completed the first year of follow-up after treatment, the proportion with inactive lesions was higher for PB than MB patients (59% *vs.* 37%) (χ^2 = 94; $P < 0.001$).

Of the 1569 due for second year follow-up after treatment, we lost 10 patients. Of these, 807 patients (51%) completed follow-up, in whom the proportion with inactive lesions was 57% in PB and 28% in MB patients (χ^2 = 63; $P < 0.001$).

Discussion

Planning and designing the U-MDT trial posed several technical and operational challenges. The proposal was thoroughly debated at various national and international technical meetings. Experts discussed the need for uniform regimen, trial design, sample size assumptions and the assessment of the outcome. Finally, MB-MDT for 6 months was proposed as the uniform regimen. Accumulated evidence indicated that side effects and toxicity for the three drugs in this combination were rare. An open trial design was selected to assess the primary outcome of relapse in the light of several practical limitations of adopting a randomized controlled trial design. These limitations include difficulties in identifying individual patients at high risk for relapse, such as patients with high bacteriological index of ≥4 and a relatively long time span for recruitment of patients for the stipulated trial. Based on the available information in the literature, a rare event such as cumulative relapse rate of 5% over a period of 5 years of follow-up, we considered a sample size of 2500 each for MB and PB patients as adequate. We defined various levels of clinical improvement of skin lesions based on standardized clinical criteria. We adopted these criteria from the WHO supported PB leprosy field trials (Single-lesion Multicentre Trial Group 1997; 2–3 Lesion Multicentre Trial Group 2001). In those trials, a scoring system to assess clinical progress was used; however, in the present study we use the same criteria without actual scores to capture clinical improvement in terms of disappearance or reduction of size of skin lesions and recovery of sensation.

We were able to recruit 2912 patients, which was very much less than anticipated enrolment of 2500 patients each in MB and PB category. In India, this could be attributed to considerable decline in new cases detected over the years. This decline could be due to operational factors or factors such as improvements in socio-economic conditions, secondary effect of vaccines (e.g. BCG) and impact of MDT or natural decline. With the integration of leprosy with general health services, the reporting mechanism for leprosy that existed during the vertical programme does not exist now. There is no active case finding. Hence not all new cases that occurred in the community might be recognized by the integrated system. In addition, the new case detection rate reported in various centres earlier might need correction in view of operational factors such as recycling, sensitivity and specificity of diagnosis, self-reporting behaviour, case detection methods and intensity, setting of targets and active case detection campaigns (Gupte *et al.* 2006). On account of MDT implementation and probable clearance of backlog, the number of new cases could be much smaller than indicated by the earlier reports at the district level. In fact, for the recent leprosy clinical trials in India, a multicentric design is being adopted with longer intake periods, to generate sufficient numbers (Single-lesion Multicentre Trial Group 1997; 2–3 Lesion Multicentre Trial Group 2001). In China, we did not expect large number of cases; however, we decided to include China, because it had different epidemiological features. It was thus not possible to enroll the desired number of patients with the current participating centres. However, on the basis of number of patients enrolled so far, we calculated the power of the trial for 5% anticipated cumulative relapse rates. Overall, for both PB and MB patients together (n = 2912), the trial had the power of 99% [91% for PB patients enrolled (n = 1777) and 77% for MB patients (n = 1135)]. WHO reviewed this issue and recommended that current participating centres increase the intake and that the trial be expanded to a few more endemic areas (WHO 2006). Already DFIT has initiated the trial in one more center in Bihar, India. Two more international centers are likely to join. Therefore, we will have adequate power for MB group as well.

Interim analysis of the U-MDT open trial indicates that U-MDT treatment is efficacious in improving the clinical status of skin lesions on the basis of clinical assessment. This efficacy is documented for both PB and MB patients. The proportion of MB patients with 'inactive lesions' (37% and 28% 1 and 2 years post-treatment, respectively) documents the efficacy of the shortened duration of treatment for MB patients. Thus, the U-MDT regimen could be effective and operationally convenient in the context of integration of leprosy into general health services. Drug compliance with a shorter duration could make it an acceptable regimen for MB patients. The proportion with inactive skin lesions observed for PB patients (59%) at the end of 1 year post-U-MDT was comparatively higher than what had been reported earlier (31%) in studies conducted for PB patients (Single-lesion Multicentre Trial Group 1997; 2–3 Lesion Multicentre Trial Group 2001). Further, clofazimine-related pigmentation of the skin was usually short-lived and acceptable to PB patients. Generally, patients readily accepted the U-MDT regimen.

The study results are promising with respect to clinical status of skin lesions. We need to follow-up the patients to assess the primary outcome of relapse rate at the end of 5 years. We expect the final results by 2014 since all the centres would complete the follow-up by 2013.

Acknowledgements

The process of developing the protocol and call for applications was facilitated by WHO/TDR. The project was initially funded by WHO. The UNICEF/UNDP/World Bank/WHO Special Programme for Research and

Training in Tropical Diseases (TDR) has been financially supporting the trial since December 2005. Novartis supplies special blister packs of 6-month uniform MDT through WHO.

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CÂMARA DOS DEPUTADOS
PRIMEIRA-SECRETARIA

Ofício 1ªSec/RI/I/nº 2327 /2018 Brasília, 3 de julho de 2018.

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Exmo. Senhor Deputado
LUCIANO DUCCI
Gabinete 427 – Anexo 4

Assunto: **resposta a Requerimento de Informação**

Senhor Deputado,

Encaminho a Vossa Excelência cópia do Aviso nº 347/2018-ASPAR/GM/MS, 25 de junho de 2018, do Ministério da Saúde, em resposta ao **Requerimento de Informação nº 3.587/2018**, de sua autoria.

Atenciosamente,

Deputado GIACOBO
Primeiro-Secretário