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Relapses in multibacillary leprosy patients: A retrospective cohort of 11 years in Colombia

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Summary
Objectives: To determine the frequency and factors associated with relapse in multibacillary leprosy.
Design: We performed a retrospective cohort study on multibacillary leprosy patients treated at Centro Dermatologico Federico Lleras Acosta between January 1994 and December 2004. By survival analysis we studied the incidence density for recurrence and bacillary index conversion. The assessment of risk factors associated with the occurrence of relapse was constructed using a Cox regression model.
Results: We included 299 cases of which 243 received WHO-MB MDT on a regular basis, and followed them up to assess the frequency of relapses. We obtained 490 person-years of follow-up and an incidence density of 6·70 relapses/100 patient-years that was higher than most of the data reported in the literature. The relapse rate was 9·80 per 100 person-years when the initial bacillary index was $\geq$ 2·0 and 5·60 relapses/100 patient-years when it was <2 ($P = 0{\cdot}03$). The relapse rate increased to 7·70/100 patient-years among those treated with WHO-MB 24 month fixed-dose, and it reduced to 5·70/100 patient-years when treated until smear negative. The variables that showed association with relapse were: initial bacillary index $\geq$ 2·0, anti-reactional treatment and clinical classification of lepromatous leprosy. For each variable, the risk was four to five times more likely to present relapse. We also found that 21 patients' BI became negative per 100 treated for 1 year with WHO-MB MDT.
Conclusions: We found a high relapse rate associated with initial high bacillary index in the Colombian population. Among the patients who received MDT on a regular basis 33 out of 165 (20%) relapsed.

Introduction

Leprosy is one of 13 major disabling diseases in the group of neglected tropical diseases; a group that includes the most common chronic infections in the poorest people on earth,

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a population that is estimated at 2·70 billion people whose income is less than US$2 per day.[1] In this context, the great effort made by the WHO to ensure the implementation of multidrug therapy (MDT) for leprosy on a global scale is invaluable.

The use of MDT has succeeded in reducing the overall prevalence of the disease, although the number of new cases has remained stable. Measuring long-term effectiveness of drugs is difficult because neither the clinical nor bacteriological evaluations are highly sensitive, nor the lack of multiplication of *Mycobacterium leprae* (*M. leprae*) in mouse foot pads at the end of treatment is proof that complete elimination of bacilli from the patient has been achieved. As with other infectious diseases, the only method to quantify the long-term effectiveness of interventions is the measurement of the rate of relapse after discontinuation of therapy.[2,3]

The relapse rate reported by different authors has been variable. The factors determining this variability could be due to: differences in the definition of relapse, in the initial bacillary index (BI), in the follow-up time of patients, the method of gathering information and possibly immunogenetic variation in different populations. Reported relapse rates in the literature have ranged between 0 and 7 per 100 person-years.[4–15]

To date we haven't found studies in Colombia that estimated the rate of relapse after MDT for multibacillary (MB) leprosy with the World Health Organization's scheme (WHO-MB). Dermatological Center Federico Lleras Acosta E.S.E. (CDFLLA) as a public entity attached to the Ministry of Health and Social Protection from Colombia, treats patients that attend by spontaneous demand or by remission, with any skin disease, and it is also an academic and research centre in dermatology. Since its creation, the institution has had a special interest in care and research related to Hansen's disease.[16] CDFLLA has been prescribing WHO-MB MDT to MB patients until smear negativity. Given the perception of a high frequency of clinical relapses in this group of patients, we designed this retrospective cohort study of patients who were diagnosed between January 1994 and December 2004 to determine the frequency and possible risk factors for relapses in MB leprosy. For this study relapse was defined as: appearance of new skin lesions or new neural symptoms with or without increase in the BI. It is important to note that in Colombia we do not use the logarithmic international Ridley-Jopling scale to measure the BI.[17] The scale is similar to that used in tuberculosis, which is semi-quantitative and the BI goes from 0 to 3.[18] This difference in definitions of BI hinders the application of knowledge derived from literature and WHO recommendations in Colombia.

In the CDFLLA, follow-up the MB patient's treatment continues until smear negativity, and then during the surveillance period of 5 years we take smears from the usual sites every 3 months. When we confirm a new case of leprosy, we explain to the patient the importance of evaluating his/her household contacts in order to detect whether there are other cases in the family group. The household contacts attend spontaneously and are evaluated by a dermatologist or a dermatology resident, who examines their whole body, explores sensitivity and assesses nerve trunks. If applicable, the relevant examination to establish or exclude the diagnosis of leprosy in all household contacts is undertaken.

Materials and Methods

PATIENTS

The retrospective cohort study includes all patients diagnosed with MB leprosy at CDFLLA in the period between January 1994 and December 2004. All those patients whose medical

records did not have the information required for the study were excluded. We reviewed a total of 1010 medical records of which 299 met the two eligibility criteria: (i) MB patients diagnosed and treated in the CDFLLA during the period 1994–2004, with comprehensive and complete clinical, histological and bacteriological records. (ii) MB patients are those with a BI of five sites studied greater than 0. In Colombia the cases with initial BI = 0 are considered MB when they have bacilli in the histological biopsy stained with Ziehl-Nielsen; all new patients have this histopathological test to ensure correct classification and in cases of suspected relapse.[18]

Note that in Colombia we do not use the logarithmic international Ridley-Jopling scale[17] to measure BI, we use the semi-quantitative Colombian scale.[18] We take smears from five sites: two ear lobes, two lesions and one from nasal mucus, spreading the material scraped from the incision onto one slide, and making circles 8 mm in diameter. With the 100× objective we search the presence of acid-fast bacilli, examining approximately 100 fields per smear to quantify every sample according to the following scale: Negative: 0 bacilli in 100 fields. 1+: less than 1 bacille/field in 100 fields. 2+: 1–10 bacilli/field in 50 fields. 3+: more than 10 bacilli/field in 20 fields. With these scoring from five sites, we calculate the BI of the patient that is obtained as the scoring average which is between 0–3.

For this study relapse was defined as: Patients who having completed the MB-MDT in a timely manner, presented new skin lesions or new neural symptoms with or without an increase in the BI compared with that at the termination of MDT.

In our centre, the increase of BI is only substantiated when it is sustainably observed in two consecutive quarterly bacteriological examinations, because this monitoring post-treatment is conducted quarterly. We believe that an increasing BI is more representative of the true bacteriological state of the patient then the quantification of bacillary load in a single site.

The analysis of the effectiveness of MDT in terms of frequency of relapses was based exclusively on the 243 patients who received chemotherapy with WHO-MB MDT.

STATISTICAL ANALYSIS

Through an analysis of survival we determined the incidence density for relapse and smear negativity. To evaluate the risk factors associated with the occurrence of relapse we constructed a Cox regression model.

We explored the effect of duration of treatment and relapse rates in order to assess which of the variables studied could be considered a risk factor for relapse. We conducted a bivariate analysis for nominal variables by the Log-Rank test and for continuous variables by Cox regression.

With regard to the interpretation of the BI, according to the Colombian scale, we took as the cut off a BI $\geq 2{\cdot}0$, which we have concluded is a high bacillary load as same as BI $\geq 3{\cdot}0$ in the Ridley-Jopling logarithmic scale.[19]

Nominal and continuous variables reclassified that were analysed were: gender, age at diagnosis, initial BI, Type 1 and Type 2 reaction, anti reactional medicines received, treatment of reactions with steroids or thalidomide, dapsone monotherapy prior to MDT, presence of household contacts diagnosed as leprosy patients, final BI and number of MDT doses received.

Results

Briefly, the cohort consisted of individuals aged between 7–80 years at diagnosis, the median was 39 years. 4·30% ($n = 13$) were less than 15 years. 70% were men. There were 53 patients who received dapsone monotherapy prior to the MDT; 243 patients received WHO-MB MDT. A total of 212 patients in the cohort (70·90%) reported at least one reaction during the course of the treatment or surveillance and among these most (73·11%) were Type 2 reactions.

The frequency of lost patients of institutional treatment was 24·75% (74 patients). Among patients who discontinued treatment, 59 were on the WHO-MB scheme, of which 71·20% had not completed 24 doses.

Regarding the outcome of 243 patients with WHO-MB MDT we found that 165 patients (68%) were regular with at least 24 doses in 36 months, three died, 59 (24·30%) discontinued treatment and 16 (6·70%) were irregular. The median duration for WHO-MB MDT was 2·77 years.

A significant proportion of patients (38%) had a high initial BI (≥2·0) and therefore, this was the cut off (BI = 2) for its assessment as a risk factor for relapse. Figure 1 shows the distribution of the cohort according to initial BI, measured with the Colombian scale and the BI of regular patients after completion of 24 doses are also shown in Figure 1.

After 24 doses of regular MDT, only 32·70% of patients had negative smears. From a total of 141 patients who received regular MDT and started with a positive BI, 82 patients (58·20%) reached smear-negativity before going into surveillance; 59 patients did not become negative, persisting with a positive BI at a low value and entered the surveillance period anyway.

The number of months of regular MDT required to achieve smear-negativity, ranged between 1 and 79 months; 20 out of 59 patients, who did not become negative during

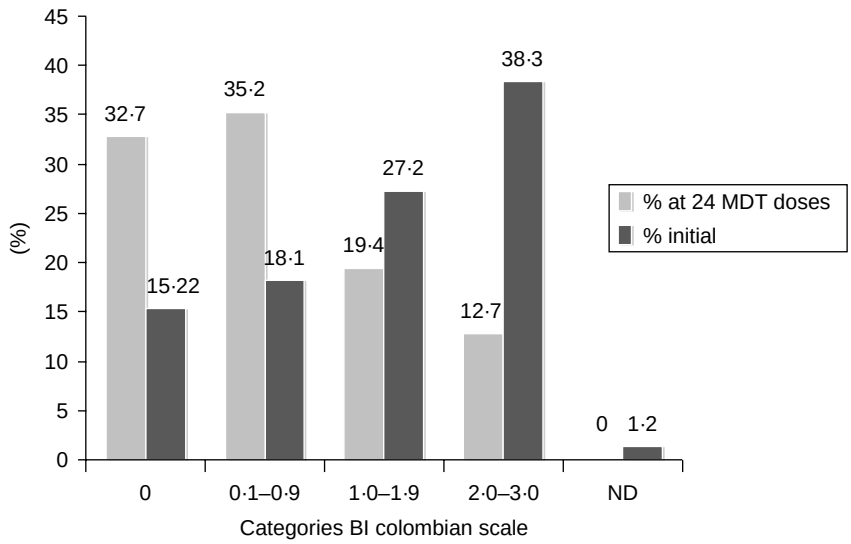

Figure 1. Distribution of patients by bacillary index categories at diagnosis and later than 24 MDT doses.

Table 1. Patients with and without relapse by number of doses received before stopped MDT

Doses Received N°	Patients N° (%)	
	Relapses	No relapses
24	11 (29·73)	26 (70·27)
25–36	15 (19·48)	62 (80·52)
37–48	5 (17·86)	23 (82·14)
49–60	2 (12·5)	14 (87·50)
61–72	0 (0·0)	5 (100)
73–84	0 (0·0)	2 (100)
Total	33 (20·0)	132 (80·0)

treatment went to into the surveillance period with a low BI, and during this surveillance period became negatives without MDT. Three of these 20 patients subsequently relapsed.

The time of follow-up post-MDT in the cohort patients, ranged from less than 1 year to 10·65 years, the median time of follow-up was 3·37 years. Among patients who received MDT on a regular basis, ($n = 165$) there were 33 relapses of the disease (Annex 1). Thirty of these patients were diagnosed as relapses due to new signs and symptoms, 54·50% ($n = 18$) with new skin lesions and 36·40% ($n = 12$) without skin lesions but neural involvement. The remaining three patients only showed new bacteriological or histopathological findings at the time they were suspected of relapse.

Table 1 show the distribution of patients who had received MDT regularly distributing by the number of doses before stopping treatment and their status of relapse or otherwise. The categories of initial BI of patients who relapsed or did not relapse is shown in Table 2.

The cohort completed a follow-up of 490 person-years (p-y), during which there were 33 events of relapse post-regular MDT, corresponding to a relapse rate of 6·70 per 100 p-y. We firmly believe than 95% confident that the true rate of relapse in the cohort is between 4·78 and 9·40 relapses per 100 p-y, making an estimate of the survival function for relapse in the cohort by the Kaplan-Meier method (Figure 2) the probability of relapse in the first 5 years post-treatment was 31·68%.

Differences were statistically significant ($P = 0·03$) in terms of relapse among groups of initial BI ≥ 2 versus initial BI <2. However, when comparing the confidence intervals (CI95%) for the two categories we found that these overlap, which may be due to the small number of relapses in the cohort (Table 3).

Table 2. Patients with and without relapse by initial bacillary index using Colombian scale

Initial BI Categories	Patients N° (%)	
	Relapses	No relapses
0	4 (7·41)	50 (92·59)
0·1–0·9	6 (10·34)	52 (89·66)
1·0–1·9	10 (31·25)	22 (68·75)
2·0–3·0	13 (61·90)	8 (38·10)
Total	33 (20·0)	132 (80·0)

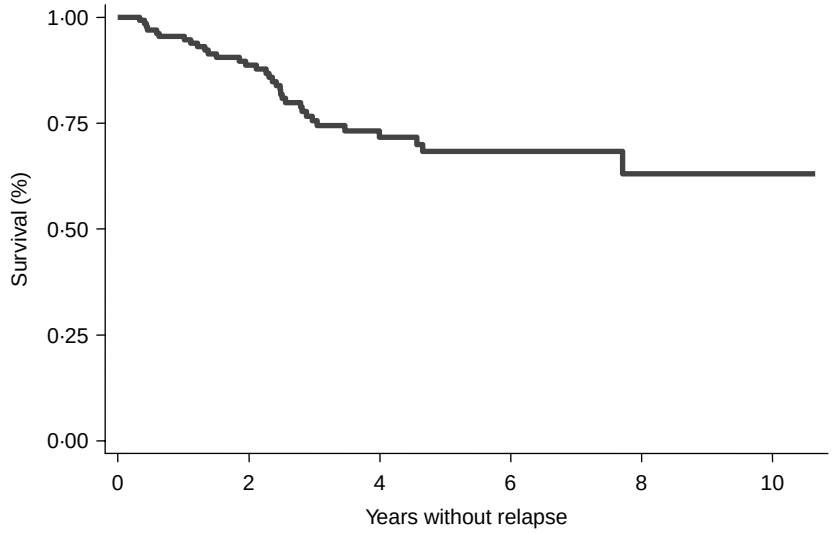

Figure 2. Survival for relapses in the cohort by Kaplan-Meier.

We found no difference in the rate of relapses according to the duration of treatment. The rate of relapses according to the clinical form of the disease showed no significant differences: for leprosy different from the polar form it was 4·49 relapses per 100 p-y while for the polar LL form it was 8·01 relapses per 100 p-y ($P = 0{\cdot}15$) (Table 3).

The comparison of the rate of relapse among patients who became the negative BI before enter surveillance versus those who did not become negative BI was not statistically significant. (Log Rank test: $P = 0{\cdot}15$) (Table 3).

Table 3. Comparison of relapse cumulative rates according to regular MDT doses, the clinical form and the initial or final BI

Variable	Follow-up p-y[a]	Relapses N	Rate X 100 p-y[a]	IC 95%	P
Total Cohort	**489·82**	**33**	**6·74**	**4·9–9·48**	
TMD Received					
> 24 doses	347·20	22	6·34	4·17–9·62	0·487
= 24 doses	142·62	11	7·71	4·27–13·93	
> 26 doses	279·33	16	5·73	3·51–9·35	0·075
≤ 26 doses	210·49	17	8·08	5·02–12·99	
< 36 doses	356·23	24	6·89	4·62–10·29	0·758
≥ 36 doses	141·69	9	6·35	3·31–12·21	
Clinical form					
Others	177·93	8	4·49	2·25–8·99	0·158
LL	311·89	25	8·02	5·42–11·87	
Initial BI					
≥ 2	**132·59**	**13**	**9·80**	**5·69–16·89**	**0·037**
< 2	**357·23**	**20**	**5·60**	**3·61–8·68**	
Ending BI					
Positive	162·08	14	8·64	5·11–14·58	
Negative	327·74	19	5·80	3·69–9·09	0·151

[a] Person-Year.

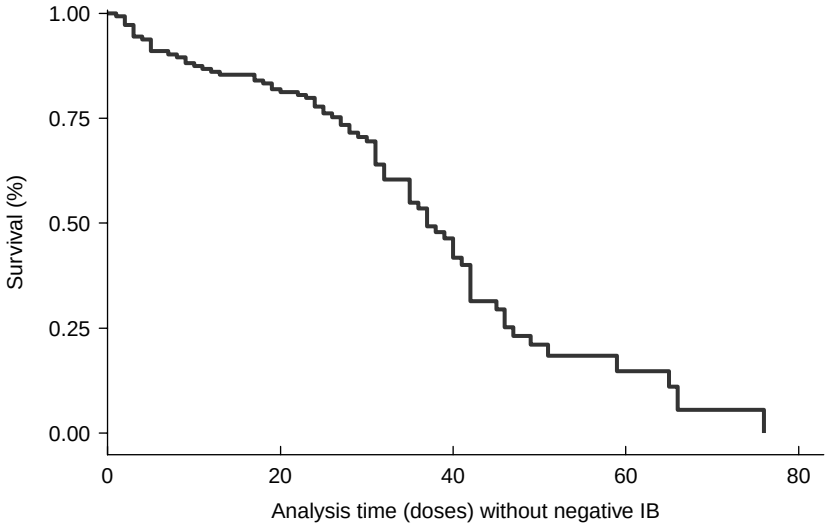

Figure 3. Survival for BI negativity in the cohort by Kaplan-Meier.

In this cohort study we documented a follow-up of 4195 doses/person, during which the BI of 82 patients became negative. With a 95% confident we are sure that true rate of BI negativity in the cohort was between 17 and 48 per 100 p-y treated.

By the Kaplan-Meier method (Figure 3), we estimated that the probability of becoming smear-negative after 24 doses of MDT is 22·30%.

In the bivariate analysis, significant association was found with the variables shown in Table 4. Although we found association with anti-reactional treatment, there was no difference by treatment type received whether it was systemic corticosteroids or thalidomide.

Including the variables in the Cox regression model, we found that only three factors were associated with the occurrence of relapses in the cohort: initial BI $\geq$ 2·0, history of anti-reactional treatment and polar lepromatous leprosy as clinical type. In this final model we found that patients with polar lepromatous leprosy are four times more likely to relapse than those with other clinical classification; that patients with an initial BI $\geq$ 2, are four times more likely to relapse than patients with an initial BI $<$ 2, and that patients with a history of anti-reactional treatment are five times more likely to relapse than those who did not take this medication (Table 5).

Discussion

The incidence density of relapses from the Colombian cohort studied, taking into account the time contributed by each person, was 6·70 relapses per 100 p-y which appears to be higher than that reported in the literature,[7–10,12–14] except the works of Gindhar in India,[11] Jamet P & Ji B in the Marchoux cohort,[15] of Gelber *et al.*,[20] Balagon *et al.*,[21] Fajardo *et al.*[22] in The Philippines and recently Shetty V *et al.* in India.[23]

Patients relapsed in this cohort, between 1 and 7 years after treatment ended. 97% of relapses were observed before 5 years of follow-up, which seems to suggest that in Colombia we should continue surveillance for 5 years and this time is sufficient to detect most cases of

Table 4. Bivariate analysis of variables for association with the relapse event. Log-Rank test for nominal variables and Cox regression for continuous variables

		p	
Factors	n	Chi^2	$Pr > Chi^2$
Gender			
Male	19	0·65	0·419
Female	14		
Age at diagnosis (years)			
< 35	15	0·08	0·777
≥ 35	18		
Initial BI			
< 1	10	1·46	0·227
≥ 1	23		
< 2	20	4·35	0·037[a]
≥ 2	13		
Final BI			
Positive	14	2·06	0·151
Negative	15		
Anti reactional treatment			
Yes	29	8·76	0·003[b]
No	3		
Anti reactional type treatment			
Thalidomide	18	0·24	0·622
Prednisolone	11		
Reaction type			
Type 1	6	1·28	0·259
Type 2	23		
Previous DDS monotherapy			
Yes	5	0·13	0·718
No	28		
Household contact with leprosy			
Yes	1	1·39	0·239
No	32		
Clinical form			
BB	4	2·99	0·393
LL	25		
BL	4		
BL clinical form			
Yes	4		0·169
No	29	1·89	
LL clinical form			
Si	25	2·08	0·149
No	8		
MDT doses received			
$= 24$	11	0·48	0·488
> 24	22		
24 ± 2	17	2·71	0·075[b]
> 26	16		
< 36	24	0·09	0·759
≥ 36	9		

[a] *Statistically significant difference Fleming-Harrington test.*
[b] *Statistically significant difference Log rank test.*

Table 5. Risk factor associated with relapse by Cox Regression model

Variable-time	Hazard ratios	Standard Error	Z	P > |Z|	CI 95%
Initial BI ≥ 2	4·294	2·801	2·23	0·026	1·196–15·423
Anti reactional treatment	4·881	3·698	2·09	0·036	1·106–21·546
Lepromatous leprosy	4·102	2·518	2·30	0·021	1·232–13·662

relapse. On the other hand, the shorter period of presentation of event can reflect reactivations caused by insufficient medication as was demonstrated by Ghindar *et al.*[11] and Shetty *et al.*[24]

Among patients who relapsed after regular MDT, a third had received 24 doses of treatment and the remaining cases relapsed despite receiving 25 to 60 doses (Table 1). Most relapses were diagnosed after receiving between 25 and 48 doses of regular treatment, which might suggest the need to assess other schemes for those who after 24 doses persist with positive smears, as proposed by Balagon *et al.*[21] Fajardo *et al.*,[22] and Shetty *et al.*;[23] and not confirm that suggested by Waters MFR[25] to administer another 24 MDT doses because persistent bacilli are not killed by this medication.

The risk factors significantly associated with the occurrence of relapse obtained by the log-rank test were: initial BI ≥ 2·0 (according to the Colombian scale, as BI ≥ 3·0 in the Ridley-Jopling logarithmic scale),[19] and anti-reactional treatment history. In turn characteristics that best predict the occurrence of relapse obtained by Cox regression model are: initial BI ≥ 2·0, and antireaccional treatment history and clinical classification as polar lepromatous leprosy.

Among patients who relapsed, the majority (69·7%) had an initial BI between 1·0 and 3·0 (according to the Colombian scale) and although at the end of treatment about half of these patients had a negative BI (45·45%), the same proportion was still positive with a low BI, between 0·1 and 0·9. It is also interesting that 60·60% of patients who relapsed had an initial BI <2·0 (according to the Colombian scale, as BI < 3·0 in the Ridley-Jopling logarithmic scale). We cannot compare our results with those published in terms of our BI because we use another scale, so we cannot know the exact proportion of patients who started with a BI >4·0 in the Ridley-Jopling scale – a factor that is repeated in several studies as associated with relapse.[2]

If one considers the difficulties in the diagnosis of leprosy, and specifically the fine line between the clinical manifestations of relapse and reactions, it is important to know who made the best diagnosis – dermatologists or seasoned leprologists. Probably the fact that in our study the evaluation of relapses was performed by trained dermatologists and microbiologists resulted in the identification of a greater proportion of relapse than might be obtained by less well-trained personnel.[26]

Given that a problem in the diagnosis of leprosy relapses is the need to be able to distinguish this from lepra reactions,[27] especially when new manifestations solely involve nerves, it is important to emphasize that in this cohort we found a high frequency of reactions (70·90%), being the predominant Type 2 reaction: erythema nodosum leprosum (73·11%).

In a recent field study conducted by Desikan in India, they found a frequency of reactions (Type 1 + Type 2) of 3·70% being the Type 1 reaction rate of 3·90% out of dimorphic cases and Type 2 reaction was found in 23·70% of LL/BL cases. Also, a higher frequency of reactions was observed in dimorphic-dimorphic leprosy cases, while in dimorphic lepromatous leprosy they found a high incidence of Type 1 and Type 2 reactions

(12·80%).[28] Scollard stated that the two most important types of reactions in leprosy can, together, affect 30% to 50% of all patients with leprosy.[29] The higher frequency of reactions in this cohort could be explained by the predominance of polar lepromatous leprosy patients (69%) with high bacillary loads; other possible explanations for these differences are: (i) population genetic differences, (ii) differences in the criteria for diagnosis of reactions, (iii) differences in the training of observers: dermatologists and dermatology residents in a specialised centre for evaluation versus general practitioners and other health personnel in field studies.[28]

Therefore, considering that in our population the initial BI are high, reactions are frequent and most patients have a polar lepromatous form of the disease, one can conclude that this is a population with increased risk of developing relapse after regular MB-MDT as shown by the analysis of the factors that were associated with relapse (Table 5). The fact that the most significant factor was the history of anti-reactional treatment received, regardless of the medication used, may suggest that this is not associated with immune suppression mediated by medication (e.g. prednisolone). We can also assume that a factor common to the reactions and relapses that could explain these two events would be the persistence of bacilli.

In this cohort we report a follow-up of 4195 dose-patient, during which we achieved smear negativity in 14 cases per 100 p-y, which means that adopting the WHO guidelines on shortening the treatment duration to 12 months could increase the risk of transmission. The BI of patients after completion of 24 doses of regular WHO-MB MDT show that only 23·75% had negative smears with this length of treatment; the rest remained positive BIs. Continuing MDT to obtain a negative BI means it is possible to achieve this objective in 58·29% of cases, even prolonging WHO-MB-MDT to 84 months.

The median time until smear-negativity – i.e. the time at which 50% of the subjects became negative – was 37 months, assuming that 24 MDT doses were taken in 24 months. An estimated 27 months are necessary for 25% of cases to achieve smear-negativity and 75% of cases would be negative after 47 months. In 19·42% of the cases smear-negativity would not be reached in spite of prolonged treatment. For these reasons we believe it would not be appropriate to reduce the duration of WHO-MB MDT schemes in our lepromatous patients.

In this regard, and considering the significant proportion of patients who not obtain a negative BI, despite conducting WHO-MDT on a regular basis, it is important to assess the viability and drug resistance of *Mycobacterium leprae* at the end of treatment of 24 doses, and to conduct comparative studies between schemes of fixed duration versus schemes until smear-negativity with viability assessment and close monitoring to detect relapse and to determine the best therapeutic option for our patients. Therefore, to achieve an impact on the BI rates of patients admitted to the Leprosy Control Programme it is important to strengthen the education for patients to alert them to the signs and symptoms of the disease, as well as to medical personnel and paramedics to ensure early detection of the disease.

A question which arises in this type of study is whether the events that we are quantifying, are true relapses, or we are faced with patients' reinfection.[30–31] In this framework today, there are molecular tools that allow us to define this situation, as has been reported in recent publications.[30–34] Objectively, this study shows several findings that suggest the possibility of diagnosing as a relapse those who really had a re-infection. First of all we can assume that to date we have not succeeded in breaking the chain of transmission of leprosy in Colombia because: we cannot demonstrate that the decrease in the detection of new cases is caused by reduction of disease transmission and there is still a proportion of leprosy reported in children, and the high number of new cases found by activities of active searching.[35–38]

The second reason is the high detection of new patients among the household contacts of leprosy cases that allow bacilli to circulate within the home. In this cohort, although not knowing the total number of household contacts evaluated, it was established that for every 10 cases of leprosy we detected a new case among household contacts. However, this figure could be increased by evaluating all household contacts.

In the Cardona-Castro study, undertaken in the leprosy control programme in Antioquia, a Colombian region of low prevalence of leprosy, the household contacts from 56 patients diagnosed with lepromatous leprosy were assessed and they found two new patients.[39] Thus, this number was three times lower than those detected in our study where this examination was specifically done by dermatologists.

Unlike Girdhar *et al.*,[11] in our study no clear conclusions were obtained regarding the need for treatment until smear-negativity and the advantages of this scheme versus the fixed duration scheme used at present. The results observed with respect to the longer duration of treatment in patients who relapsed versus those who did not, taking into account only those who became bacillary negative, could suggest that achieving a larger reduction of bacillary load in this group would reduce the risk of relapse, or that a longer duration of treatment in a study in a given period, we would have a shorter follow-up and therefore it would be less likely to detect relapses. It is therefore necessary to conduct prospective studies in the Colombian population, comparing the effectiveness of treatment with fixed dose versus treatment until smear-negativity.

Since this study presents the first real data of patients with relapses of leprosy in a Colombian population, it is important to keep in mind when taking therapeutic decisions, which risk factors associated with relapse are more frequent in this population than reported in other countries, which explains the higher frequency of relapses in our study, compared with data previously reported in the literature.[40]

It is essential to strengthen patients' surveillance after treatment to detect recurrence, also to evaluate periodically household contacts to detect new cases and avoid possible re-infection of the index case.[31]

This study has certain strengths and certain weaknesses. Among the strengths we can highlight that the study was conducted in a specialist dermatology centre, where patients are followed monthly during treatment and quarterly during follow-up after treatment. In each of these controls a comprehensive assessment is conducted with cutaneous, neurological and bacteriological evaluation. The number of patients included in the study was adequate and the median follow-up post-treatment was 3·4 years: higher than many of the studies reported in the literature.

The weaknesses include the fact that it is a retrospective study that excluded a significant proportion of patients due to lack of data in the clinical records and lack of adherence of patients to treatment and during follow-up after treatment. The loss of adhesion is a real problem in a prolonged and multidrug treatment as that used in leprosy; however, we tried to obviate this by using the analysis of survival and using the time that each individual contributed to the study.

Finally, despite the impact of MDT on the prevalence of leprosy we, as most authors agree, question the impact on the incidence of the disease, which has made it difficult to obtain the goal of the elimination as a public health problem. It is also important to continue to allocate resources to this programme in endemic countries, especially in the 'post-elimination' era, since the quality of training of medical and paramedical personnel will decrease the detection of cases in the population.

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Authors' Contributions

Martha Inirida Guerrero, Sandra Muvdi and Clara Ines León conceived and designed the study. Martha Inirida Guerrero, Sandra Muvdi and Clara Ines León analysed the data and wrote the paper. Martha Inirida Guerrero, Sandra Muvdi and Clara Ines León reviewed and approved the paper.

Ethical Statement

The data used in this study are part of routine work and only secondary data were used; no personal identifiers were disclosed. The Institutional committees of Ethical and Scientific have approved the utilisation of data collected and warrant that were used exclusively for the surveillance programme and that every patient's confidentiality is protected.

Conflict of Interest

The authors state no conflict of interest.

References

[1] Hotez P, Molyneux D, Fenwick A *et al.* Control of Neglected Tropical Diseases. *N Engl J Med*, 2007; **357**: 1018–1027.

[2] Baohong J. Does there exist a subgroup of MB patients at greater risk of relapse after MDT? *Lepr Rev*, 2001; **72**: 3–7.

[3] Norman G, Joseph G, Richard J. Relapses in multibacillary patients treated with multi-drug therapy until smear negativity: findings after twenty years. *Int J Lepr Other Mycobact Dis*, 2004; **72**: 1–7.

[4] Shen J, Liu M, Zhang J *et al.* Relapse in MB leprosy patients treated with 24 months of MDT in South West China: a short report. (Letter). *Lepr Rev*, 2006; **77**: 219–224.

[5] Shaw IN, Christian M, Jesudasan K *et al.* Effectiveness of multidrug therapy in multibacillary leprosy: a long-term follow-up of 34 multibacillary leprosy patients treated with multidrug regimens till skin smear negativity. *Lepr Rev*, 2003; **74**: 141–147.

[6] Ho CK, Lo KK. Epidemiology of leprosy and response to treatment in Hong Kong. *Hong Kong Med J*, 2006; **12**: 174–179.

[7] Chen X-S, Li W-Z, Jiang C, Ye G-Y. Studies on risk of leprosy relapses in China: relapse after treatment with multidrug therapy. *Int J Lepr Other Mycobact Dis*, 1999; **67**: 379–387.

[8] Marchoux Chemotherapy Study Group. Relapse in multibacillary leprosy patients after stopping treatment with Rifampin-containing combined regimens. *Int J Lepr Other Mycobact Dis*, 1992; **60**: 525–535.

[9] Becx-Bleumink M. Relapses among leprosy patients treated with multidrug therapy: experience in the leprosy control program of the all Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia; practical difficulties with diagnosing relapses; occupational procedures and criteria for diagnosing relapses. *Int J Lepr Other Mycobact Dis*, 1992; **60**: 421–435.

[10] Jesudasan K, Vijayakumaran P, Manimozhi N, Jayarajan T. Absence of relapse within 4 years among 34 multibacillary patients with high BIs treated for 2 years with MDT. *Int J Lepr Other Mycobact Dis*, 1996; **64**: 133–135.

[11] Girdhar BK, Girdhar A, Kumar A. Relapses in multibacillary leprosy patients: effect of length of therapy. *Lepr Rev*, 2000; **71**: 144–153.

[12] Vijayakumaran P, Jesudasan K, Manimozhi N. Fixed-duration therapy (FDT) in multibacillary leprosy; efficacy and complications. *Int J Lepr Other Mycobact Dis*, 1996; **64**: 123–127.

[13] Li HY, Hu LF, Huang WB *et al.* Risk of relapse in leprosy after fixed-duration multidrug therapy. *Int J Lepr Other Mycobact Dis*, 1997; **65**: 238–245.
[14] Gebre S, Saunderson P, Byass P. Relapses after fixed duration multiple drug therapy: the AMFES cohort. *Lepr Rev*, 2000; **71**: 325–331.
[15] Jamet P, Ji B, Marchoux Chemotherapy Study Group. Relapse after long-term follow up of multibacillary patients treated with WHO multidrug regimen. *Int J Lepr Other Mycobact Dis*, 1995; **63**: 195–201.
[16] Espinosa G. *Federico Lleras Acosta: La guerra contra lo invisible*. Panamericana editorial, Bogotá, 1998.
[17] Ridley DS. The bacteriological interpretation of skin smears and biopsies in leprosy. *Trans R Soc Trop Med Hyg*, 1955; **49**: 449–452.
[18] Guerrero MI, Ricaurte O, León CI *et al. El laboratorio en lepra: Bacteriología y Patología. Red Nacional de Laboratorios*. INS editorial, Bogotá, 1992.
[19] Colorado CL, Sánchez G, Guerrero MI, León CI. Reliability and agreement of two smear reading scales for classification and monitoring of multidrug therapy in leprosy patients. *Biomedica*, 2011; **31**: 403–409.
[20] Gelber RH, Balagon VF, Cellona RV. The relapse rate in MB leprosy patients treated with 2-years of WHO-MDT is not low. *Int J Lepr Other Mycobact Dis*, 2004; **72**: 493–500.
[21] Balagon MF, Cellona RV, Cruz E *et al.* Long-term relapse risk of multibacillary leprosy after completion of 2 years of multiple drug therapy (WHO-MDT) in Cebu, Philippines. *Am J Trop Med Hyg*, 2009; **81**: 895–899.
[22] Fajardo TT, Villahermosa L, Pardillo FE *et al.* A comparative clinical trial in multibacillary leprosy with long-term relapse rates of four different multidrug regimens. *Am J Trop Med Hyg*, 2009; **81**: 330–334.
[23] Shetty VP, Wakade AV, Ghate SD, Pai VV. Clinical, bacteriological and histopathological study of 62 referral relapse cases between Jan 2004 and Dec 2009 at the Foundation for Medical Research, Mumbai. *Lepr Rev*, 2011; **82**: 235–243.
[24] Shetty VP, Wakade AV, Ghate SD, Pai VV *et al.* Clinical, histopathological and bacteriological study of 52 referral MB cases relapsing after MDT. *Lepr Rev*, 2005; **76**: 241–252.
[25] Waters MF. Relapse following various types of multidrug therapy in multibacillary leprosy. *Lepr Rev*, 1995; **66**: 1–9.
[26] Chandra R. Role of a dermatologist in the post-elimination era. *Lepr Rev*, 2007; **78**: 43–44.
[27] Linder K, Zia M, Kern WV *et al.* Relapses vs. reactions in multibacillary leprosy: proposal of new relapse criteria. *Trop Med Int Health*, 2008; **13**: 295–309.
[28] Desikan KV, Sudhakar KS, Tulasidas I, Rao PV. Observations on reactions of leprosy in the field. *Indian J Lepr*, 2007; **79**: 3–9.
[29] Scollard DM, Adams LB, Gillis TP *et al.* The continuing challenges of leprosy. *Clin Microbiol Rev*, 2006; **19**: 338–381.
[30] Oskam L, Dockrell HM, Brennan PJ *et al.*; IDEAL Consortium. Molecular methods for distinguishing between relapse and reinfection in leprosy. *Trop Med Int Health*, 2008; **13**: 1325–1326.
[31] da Silva Rocha A, Cunha Dos Santos AA, Pignataro P *et al.* Genotyping of *Mycobacterium leprae* from Brazilian leprosy patients suggests the occurrence of reinfection or of bacterial population shift during disease relapse. *J Med Microbiol*, 2011; **60**: 1441–1446.
[32] Torres JF, Colorado C, Gamboa LA *et al.* Genotyping of Colombian *Mycobacterium leprae* for determining patterns of disease transmission. *Rev Salud Pública (Bogotá)*, 2009; **11**: 3–13.
[33] Weng X, Wang Z, Liu J *et al.* Identification and distribution of *Mycobacterium leprae* genotypes in a region of high leprosy prevalence in China: a 3-year molecular epidemiological study. *J Clin Microbiol*, 2007; **45**: 1728–1734.
[34] Young SJ, Ponnighaus JM, Jain S *et al.* Use of short tandem repeat sequences to study *Mycobacterium leprae* in leprosy patients in Malawi and India. *PLoS Negl Trop Dis*, 2008; **2**: e214.
[35] Guerrero MI, Plazas N, León CI. Situación de la lepra en Colombia: un análisis crítico. *Biomédica*, 2000; **20**: 266–271.
[36] Ochoa E, Abreu A. Vigilancia de la lepra en situaciones de baja prevalencia Rev. *Panam Salud Pública/Pan Am J Public Health*, 2001; **9**: 94–101.
[37] Rodríguez G, González R, González D *et al.* Búsqueda activa de lepra y de otras enfermedades de la piel en escolares de Agua de Dios. Colombia. *Rev Salud Pública (Bogotá)*, 2007; **9**: 430–438.
[38] Moet FJ, Schuring RP, Pahan D *et al.* The prevalence of previously undiagnosed leprosy in the general population of Northwest Bangladesh. *PLoS Negl Trop Dis*, 2008; **2**: e198.
[39] Cardona-Castro N, Restrepo-Jaramillo S, Gil de la Ossa M, Brennan PJ. Infection by *Mycobacterium leprae* of household contacts of lepromatous leprosy patients from a post-elimination leprosy region of Colombia. *Mem Inst Oswaldo Cruz*, 2005; **100**: 703–707.
[40] Lockwood D. Leprosy. *Clin Evid*, 2006; **15**: 1079–1087.

Annex 1
Description of 33 Relapses Cases

ID	Year	# Hansen	# HC	Sex	Classification	Initial BI	BI at 24 doses	Final BI	BI Relapse	MDT Months	MDT Doses	MDT Years	MDT Stoped	Date Relapse	Follow-up
18	1994	4153	5653058	M	LL	1·30	0·00	0·00	0·00	25	25	2·2	29/04/1996	10/12/1996	10·492
38	1994	4189	24109727	F	LL	2·20	0·00	0·00	0·00	24	24	2·0	1/11/1996	26/01/1999	9·603
23	1994	4123	80393003	M	LL	0·80	0·00	0·00	0·00	24	24	2·0	1/08/1995	13/01/1998	12·411
27	1994	4154	24233611	F	LL	1·00	0·00	0·00	0·00	27	24	2·3	1/01/1997	01/01/2000	5·308
31	1994	4228	91439134	M	LL	2·20	0·80	0·00	0·00	36	36	2·9	1/09/1996	01/04/1997	10·314
40	1995	4198	79135945	M	LL	3·00	0·00	0·00	0·00	24	24	2·1	21/01/1997	20/05/1997	7·550
43	1995	255	21163636	F	LL	0·00	0·00	0·00	0·00	24	24	1·9	1/08/1997	01/05/2000	10·231
53	1995	4233	5735955	M	BL	0·00	0·00	0·00	0·00	24	24	2·0	1/10/1997	01/04/1999	9·239
86	1996	4251	20480855	F	LL	1·00	0·80	0·00	0·00	25	25	2·3	1/06/1998	21/09/1999	9·461
114	1997	4309	26614415	F	LL	1·60	1·00	0·00	0·00	59	41	5·6	29/10/2002	15/12/2003	4·825
131	1998	1576	20111991	F	BL	0·80	0·00	0·00	0·00	24	24	2·0	7/12/2000	28/05/2003	6·744
197	2000	2993	17014354	M	BB	0·00	0·00	0·00	0·00	28	25	2·3	6/02/2003	16/05/2005	4·650
226	2000	4602	39371	M	BL	0·00	0·00	0·00	0·00	24	24	1·8	22/02/2002	31/08/2004	5·517
258	2002	4502	41603270	F	BB	0·80	0·00	ND	0·00	26	26	2·2	4/03/2004	01/07/2006	3·544
280	2003	4549	53039038	F	BB	1·83	0·00	ND	0·00	24	24	2·0	1/07/2005	01/08/2007	2·278
33	1994	4168	2192974	M	LL	0·80	0·40	ND	0·40	42	36	3·5	17/12/1997	28/05/2000	7·506
138	1998	4343	28976300	F	LL	0·83	0·60	ND	0·40	30	29	2·6	1/09/2000	01/09/2001	4·539
26	1994	4140	5956371	M	LL	2·00	0·80	0·80	0·80	43	41	3·6	23/05/1997	01/05/2001	6·192
48	1995	4212	34984207	F	LL	2·60	0·40	0·80	0·80	47	45	4·1	1/03/1999	01/01/2002	6·611
50	1995	4226	79266583	M	LL	1·00	0·80	0·00	0·80	41	39	3·3	1/09/1998	01/12/1998	8·311
60	1995	4244	3009600	M	LL	1·80	0·80	0·40	0·80	27	27	2·3	5/03/1998	28/08/1999	6·350
52	1995	4230	37932040	F	LL	1·60	0·80	0·40	0·80	29	29	2·5	1/03/1998	01/02/2000	9·650
46	1995	4200	28418078	F	LL	3·00	0·80	0·40	0·80	34	33	3·1	31/01/1998	03/07/2001	6·819
61	1995	4242	19348410	M	LL	2·00	1·20	0·80	0·80	55	50	4·6	1/07/2000	01/05/2002	2·369
92	1996	4274	93117411	M	BB	0·80	0·80	0·00	0·80	27	26	2·3	25/09/1998	01/03/1999	5·681
85	1996	4248	3259459	M	LL	2·10	2·40	0·20	1·20	40	40	3·4	26/05/1999	05/03/2002	8·339
122	1997	4321	21081206	F	LL	2·66	1·60	0·20	1·20	36	36	3·0	1/09/2000	21/01/2003	7·214
169	1998	4505	79103674	M	LL	1·00	0·80	0·20	1·40	26	24	2·2	1/12/2000	12/02/2002	6·925
141	1998	4347	91432342	M	LL	2·66	1·80	0·20	1·40	53	51	4·6	27/08/2002	01/08/2005	4·958
159	1998	4381	14321629	M	BL	1·20	1·80	0·20	1·80	28	28	2·4	1/03/2001	01/09/2005	5·442
314	2000	4418	17305588	M	LL	2·20	2·00	0·20	2·00	24	24	2·0	1/01/2002	12/05/2003	3·597
191	1999	4486	93289406	M	LL	2·50	2·40	0·20	2·20	26	26	2·3	1/03/2002	01/10/2006	5·669
286	2002		16821873	F	LL	2·60	2·60	0·20	2·20	31	31	2·8	2/11/2004	28/03/2005	0·503