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Research article

Patterns and determinants of treatment completion and default among newly diagnosed multibacillary leprosy patients: A retrospective cohort study

Veincent Christian F. Pepito [a,b,*], Arianna Maever L. Amit [a,b], Rae Erica D. Samontina [a,b], Sarah Jane A. Abdon [a,c], David Norman L. Fuentes [a,d], Ofelia P. Saniel [a,e]

[a] College of Public Health, University of the Philippines Manila, Manila, Philippines
[b] School of Medicine and Public Health, Ateneo de Manila University, Pasig City, Philippines
[c] College of Medicine, San Beda University, Manila, Philippines
[d] Institute for Neurosciences, St. Luke's Medical Center, Quezon City, Philippines
[e] Symmetrix Research Consultancy Company, Manila, Philippines

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ABSTRACT

Background: Poor treatment adherence among leprosy patients contribute to relapse, development of antimicrobial resistance, and the eventual plateauing of the prevalence and incidence of leprosy not just in the Philippines, but also worldwide. For this reason, we aimed to identify the patterns and determinants affecting treatment completion and default among multibacillary leprosy patients.

Methods: We conducted a retrospective cohort study involving three large hospitals in Metro Manila, Philippines. Patients who started the World Health Organization - Multiple Drug Therapy for multibacillary leprosy between January 1, 2007 and December 31, 2013 were included in the study. Selected socio-demographic and clinical data were abstracted from the patient treatment records. Survival analysis and proportional hazards regression were used to analyze the data.

Results: Records of 1,034 patients with a total follow-up time of 12,287 person-months were included in the analysis. Most patients were male, younger than 45 years old, had an initial bacterial index between 1 and 4, and were residents of Metro Manila. Less than 20% had their treatment duration extended to more than 12 months. Treatment adherence of the patients was poor with less than 60% completing treatment. Most patients complete their treatment within 12 months, but treatment duration may be extended for up to three years. Patients who default from treatment usually do so a few months after initiating it. After adjusting for other variables, hospital, initial bacterial index, and non-extended treatment duration were associated with treatment completion. These factors, in addition to age, were also found to be associated with treatment default.

Conclusion: This study provides quantitative evidence that there might be marked variations in how doctors in particular hospitals manage their patients, and these findings underscore the need to revisit and re-evaluate clinical practice guidelines to improve treatment outcomes and adherence.

1. Introduction

Poor treatment adherence among leprosy patients is associated with relapse and the occurrence of antimicrobial resistance [1]. It has also been reported to contribute to the plateauing incidence and prevalence of leprosy in the Philippines [2], and worldwide [3, 4, 5, 6]. A perceived reason for poor treatment adherence is the long duration of the World Health Organization (WHO) multiple drug therapy (MDT) regimen, lasting a year for multibacillary leprosy patients [7, 8], which could even be extended for up to three years [9, 10]. In addition to the long duration of treatment, a host of psychosocial, economic, medical and health service, as well as personal factors were found to affect treatment adherence [11]. Two earlier reviews reported the following factors to be associated with poor treatment adherence: socio-economic status; educational attainment; gender; alcohol consumption; knowledge about leprosy; stigma associated with the disease; cultural factors; transportation costs;

* Corresponding author.
E-mail address: vcfpepito12345@gmail.com (V.C.F. Pepito).

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remoteness of residence; financial concerns; adverse effects of MDT; source of MDT; MDT drug shortages; poor relationship between patient and healthcare provider; and occurrence of leprosy reactions [1, 12].

A systematic review of factors associated with poor treatment adherence showed that cohort studies are not frequently used in studying this phenomena, not to mention, the use of survival analysis to analyze treatment adherence data [12]. Survival analysis is an analytic tool that deals with time-to-event data, appropriate for studying varying lengths of follow-up time to an event of interest [13]. In studying the determinants of treatment adherence, cohort studies are preferred over the more commonly-used cross-sectional or case-control designs, as the former research design allows examination of temporal direction between exposure and outcome [14]. Furthermore, the benefit of using of survival analysis to analyze treatment adherence data lies in its ability to account for varying treatment durations due to defaulting (i.e., dropping out), extending treatment, or irregular intake of MDT. Survival analysis to study determinants of treatment adherence has been used to analyze data on major depressive disorders [15], and on tuberculosis [16, 17] but none on leprosy, let alone leprosy among Filipino patients. In the Western Pacific Region, the Philippines has the highest incidence of leprosy, with around 1,700 new cases being diagnosed each year [18].

Considering the lack of studies on treatment adherence among leprosy patients, this study investigates treatment completion and defaulting patterns by using survival analysis. The study also examines the factors that are associated with treatment completion and treatment default among newly diagnosed multibacillary leprosy patients in selected hospitals in Metro Manila, Philippines.

2. Methods

2.1. Study design, population and variables

We utilized a retrospective cohort study by reviewing the clinic records of all newly diagnosed multibacillary leprosy patients aged 15 and above who commenced WHO-MDT between January 1, 2007 and December 31, 2013 in three large hospitals (A, B, and C) in Metro Manila, Philippines. Using the patient charts, we 'followed' them up until the end of their treatment, or until March 1, 2015, whichever came first. We included all patients who met the criteria and for whom we had access to their records to ensure that we have adequate sample size for our analyses.

From the patient records, we were given permission to collect the following data: hospital where they got treatment; age; sex; place of residence (i.e., Metro Manila or outside); estimated treatment duration (from the start of treatment to date when they stopped taking MDT); treatment outcome (i.e., completed treatment, defaulted, transferred-out, died, or still under treatment by March 1, 2015); and recorded bacterial index (BI) readings (i.e., initial and subsequent BI data).

2.2. Data management and analysis

To facilitate analyses of possible linear trends, we assigned 'scores' to quantitative categorical variables, such as age of patient and BI. Using the midpoint of each age group as 'score', we categorized the age of patient into three age groups (15–29, 30–44, and 45 and above) to ensure adequate sample size per strata [19]. Owing to substantial missing data on subsequent BI measurements, only the initial BI reading was included in this analysis. The initial BI data was recoded into three categories corresponding to the following cut-off values: zero (0); low (1–3); and high BI [4, 5, 6] which were assigned 'scores' of 0, 2, and 5, respectively.

The hospitals included in this study have similar definitions for treatment completion but had varying definitions for treatment default [9]. Therefore, to ensure consistency, we defined treatment completion as a patient who has been declared by the hospital as having completed the MDT, as long as they completed the minimum of 12 doses of treatment taken over a maximum of 18 months; if the treatment is extended to 18 months, all the doses should be taken over a 24-month period, and so on.

On the other hand, treatment default is defined as a patient who has not completed treatment within the prescribed duration with a six-month grace period (e.g., if a patient failed to complete 12 MDT doses in 18 months, then that person is considered a defaulter). This definition was also applied to patients whose treatment duration was extended to more than 12 months (e.g., if a patient's treatment was extended to 24 MDT doses upon the recommendation of his/her physician but failed to take all 24 doses in 30 months, then the patient will also be considered a defaulter). While the date of treatment completion should be recorded in the patient charts and/or logbooks, this data was not often found in either the patient chart or clinic logbook, especially among defaulters. To address this problem, we assumed that the date of patient default was the projected date when the patient would have consumed all the medicines received during his/her last visit to the clinic. The assumption was one blister pack would last 28 days (e.g., if the patient last visited on January 31, 2014, and has only claimed an MDT pack for one month, then the date of default will be listed as February 28, 2014).

We performed survival analysis and conducted separate analyses for treatment completion and treatment default. If the outcome for the analyses was treatment completion, patients who experienced other outcomes (e.g., died, defaulted, transferred-out, and in-treatment) were censored. Similarly, if the outcome for the analyses was treatment default, those who experienced other outcomes (e.g., died, completed treatment, transferred-out and in-treatment) were likewise censored. For both outcomes, we considered the following exposure variables: age; sex; place of residence; the hospital where they got treatment; initial bacterial index; and treatment extension. The distribution of the study participants according to categories of each exposure variable and the outcome variable were examined. Kaplan-Meier curves were used to describe treatment completion and defaulting patterns. We used number of months as the time scale for the analysis of duration of treatment adherence. The rates of occurrence of each outcome were determined for each level of the different exposure variables. Any difference in the survival functions between each level of the exposure variable was assessed using the log-rank test [20]. The crude rate ratio for each exposure was determined using the Mantel-Haenszel method. Once the crude rate ratio for each exposure variable was estimated, patients with missing data for the relevant variables were dropped from subsequent analyses. Afterwards, we used Cox proportional hazards regression to study the effect/s of the exposures on the outcome variables [21]. For the variables age and BI, we performed tests for departure-from-linearity-assumption using the likelihood ratio test. We formally tested the proportional hazards assumption of each resulting model by assessing their Schoenfeld residuals [22]. Should the proportional hazards assumption be violated in any of the models, Lexis expansion was used to stratify the follow-up time into intervals such that the proportional hazards assumption is satisfied [23]. In this case, separate Cox regression models were made for each interval. For all statistical tests, a level of significance of 0.05 was used [24]. Data were initially encoded in EpiInfo 3.5.4 [25], while cleaning and data analyses was carried out in Stata/IC 14.0 [26].

2.3. Ethics

Only anonymized data were accessed and collected; thus, it was unnecessary to obtain informed consent from individual patients. This study has received ethical approval from the University of the Philippines Manila Research Ethics Board (Reference No.: UPMREB 2015-092-UND). The study has also received ethics approval from each of the participating hospitals; however, the names of the participating hospitals are not disclosed to maintain their anonymity.

3. Results

3.1. Description of study participants

The cohort consisted of 1,034 records of newly diagnosed multibacillary leprosy patients from the three hospitals that were included in the study. These patients had a total of 12,286.6 person-months of observation time and the duration of follow-up ranged from 0 to 39.9 months. Although the number of new leprosy patients seen in each hospital per year was not available, we describe the patients according to a few demographic and relevant clinical characteristics (Table 1). Around three-fourths of the patients were male, while more than two-thirds have consulted Hospital C. The age of the patients ranged from 15 to 90 years old, but most were below 45 years old. Initial Bacterial Index (BI) varied from 0 and 6+, with 396 (38.3%) having low initial BI, and almost a similar number, 391 (37.8%), having high initial BI. From the 391 patients who had high initial BI, 103 (26.3%) were advised by their physician to extend treatment. These 103 patients, together with 74 others, made up the 177 (17%) patients in the entire cohort who were advised by their physician to extend duration of treatment to 18, 24, 30 or 36 months. This treatment duration is beyond the 12 months of treatment prescribed by the WHO. Regardless of treatment duration, around 57% of the patients completed treatment, and 37% defaulted; the rest experienced other outcomes (i.e., died, 'transferred out' to other treatment facilities, or were still in-treatment as of March 1, 2015).

Table 1. Distribution of study participants by selected characteristics (n = 1,034).

Variable	Frequency (%)
Hospital	
A	238 (23.0)
B	99 (9.6)
C	697 (67.4)
Age group	
15–29	358 (34.6)
30–44	386 (37.3)
45+	290 (28.1)
Sex of Patient	
Male	769 (74.4)
Female	265 (25.6)
Place of Residence	
Within Metro Manila	633 (61.2)
Outside Metro Manila	401 (38.4)
Initial Bacterial Index	
0	139 (13.4)
1–3	396 (38.3)
4-6+	391 (37.8)
Missing	108 (10.4)
Year started treatment	
2007	94 (9.1)
2008	149 (14.4)
2009	140 (13.5)
2010	197 (19.1)
2011	172 (16.6)
2012	151 (14.6)
2013	131 (12.7)
Treatment extension	
No treatment extension	857 (82.9)
Yes, treatment extended	177 (17.1)
Treatment outcome	
Completed Treatment	590 (57.1)
Died while in treatment	5 (0.5)
Transfer-out	38 (3.7)
Defaulted/dropped-out	383 (37.0)
In-treatment as of March 1, 2015	18 (1.7)

3.2. Patterns and determinants of treatment completion

The median time-to-treatment-completion was 13.4 months (Figure 1). This curve shows the cumulative probability of treatment completion among those who completed MDT regardless of treatment duration. In this figure, each step increase in the curve indicates a patient completing treatment, while black marks indicate patients who have experienced outcomes other than treatment completion (i.e., censored observations). Most of the patients were treated for 12 months, but there were also some who completed treatment beyond the prescribed 12-month period as decided by their physician. The large increase shortly after the 24th month represent those patients whose treatment duration was extended to 24 months and who completed the treatment. The longest recorded duration of treatment was 39.9 months. Without controlling for other variables, and among the exposure variables studied, the hospital where patients got treatment ($p < 0.01$), sex ($p < 0.01$), initial BI ($p < 0.01$), and treatment extension status ($p < 0.01$) were all significantly associated with treatment completion (Table 2).

Prior to doing multivariate analysis, we excluded some 108 (10.4%) patients who did not have any data for initial BI. Thus, in the multivariate analysis, we only included data from 926 (89.6%) patients who had complete data for all the exposure variables of interest. The proportional hazards model for treatment completion showed that after adjusting for potential confounders, there was strong evidence that the hospital where treatment was obtained, initial BI, and treatment extension were all associated with treatment completion (Table 3). Specifically, patients from Hospital C had 28% lower instantaneous rate of treatment completion (adjusted hazard ratio (aHR): 0.72; 95% Confidence Interval (CI): 0.59–0.87) compared to those from Hospital A. Similarly, patients whose treatment was extended had 98% lower instantaneous rate of treatment completion (aHR: 0.02; 95% CI: 0.01–0.04) compared to those whose treatment was not extended. Furthermore, the relationship between initial BI readings and treatment completion also did not show a departure from the linearity assumption ($p = 0.58$), hence a common hazard ratio is reported. Each unit increase in initial BI reading translated to around 7% (aHR: 0.93; 95% CI: 0.89–0.98) decrease in the instantaneous rate of treatment completion. Lastly, the relationship between age group and treatment completion did not show departure from the linearity assumption ($p = 0.89$). Thus, a common hazard ratio (aHR: 1.00; 95% CI (CI): 0.99–1.00) estimating a 0.005% decrease in the instantaneous rate of treatment completion per unit increase in age is shown in the table. There was no strong evidence that the proportional hazards assumption was violated in this model ($p = 0.20$).

3.3. Patterns and determinants of treatment default

Many patients who dropped-out from treatment did so within a few months after initiating it as shown by the steep rise early in the follow-up (median time to default = 3.6 months; Figure 2). In this figure, each step increase in the curve indicates a patient defaulting from treatment, while black marks indicate patients who have experienced outcomes other than treatment default. The last patient to drop-out of treatment did so after about 26 months of follow-up, after he/she failed to finish the treatment after his/her treatment duration was extended to 24 months. Unlike Figure 1, the cumulative probability of treatment default never reached 1 in this Figure because the person with the longest observation time (i.e., at 39.9 months) did not default from treatment; the patient actually completed treatment. Without controlling for other variables and among the variables considered, only treatment extension status was strongly associated with treatment default ($p < 0.01$). Specifically, patients whose treatment was not extended had significantly higher instantaneous rate

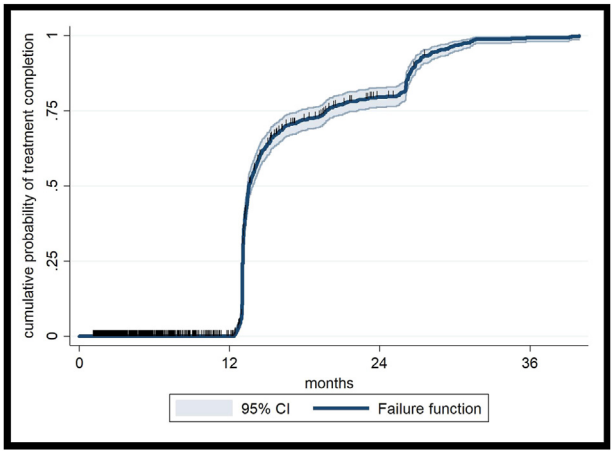

Figure 1. Treatment completion pattern of the cohort (n = 1,034).

of treatment default compared to those whose treatment was extended (Table 4).

In the initial model for this outcome, the proportional hazards assumption was violated ($p < 0.01$). Hence, we split follow-up time into the first six months of treatment, and the subsequent 6.1–39.9 months of observation. To identify the determinants of treatment default for the first six months of follow-up, respondents from Hospital B or those who had treatment extension, were excluded in the analysis for the reason mentioned above. For the first six months of follow-up, there was no departure from the linearity assumption for the association between BI and treatment default ($p = 0.21$); thus, a common hazard ratio (aHR: 1.02; 95% CI: 0.95–1.10) is reported. After adjusting for confounding variables, there was a 2% increase in the instantaneous rate of treatment default per unit increase in initial bacterial index, but this result was not statistically significant. In contrast, there was a departure from the linearity assumption between age and treatment default ($p = 0.04$). For this reason, age-specific hazard ratios are presented (Table 5). For the first six months of follow-up, there was a strong evidence that being 30–44 years old was protective (aHR: 0.72; 95% CI: 0.53–0.99) against treatment default. There was no strong evidence that the model for the first six months of follow-up violated the proportional hazards assumption ($p = 0.49$).

For six months or longer follow-up, we included in the analysis patients from Hospital B and those who had treatment extension. There was strong evidence that after adjusting for confounders, instantaneous rates of treatment default differ by hospital, initial bacterial index, and treatment extension. Specifically, the instantaneous rate of treatment default was higher in Hospital B (aHR: 2.80; 95% CI: 1.08–7.30) as compared to Hospital A. There was no departure from the linearity assumption for initial bacterial index ($p = 0.15$), and so a common hazard ratio (aHR: 1.15; 95% CI: 1.03–1.29) was used to describe a 15% increase in the instantaneous rate of treatment default per unit increase in bacterial index reading. Likewise, there was no departure from the linearity assumption for age, and a common hazard ratio (aHR: 1.00; 95% CI: 0.98–1.01) is reported to describe the 0.003% decrease in the instantaneous rate of treatment default per year increase in age. Lastly, the instantaneous rate of treatment default was 81% lower (aHR: 0.19; 95% CI: 0.10–0.36) among those whose treatment was extended compared to those whose treatment was not extended. There was no strong evidence that the proportional hazards assumption was violated by the model for this period of follow-up ($p = 0.18$).

4. Discussion

This study shows that treatment adherence of newly diagnosed multibacillary leprosy patients in selected hospitals in Metro Manila, Philippines is unsatisfactory, with less than 60% completing treatment and almost 40% defaulting from it. The study also demonstrates that treatment duration of leprosy patients is sometimes extended, disregarding WHO guidelines [7]. Results also show that many patients who leave treatment did so in the first few months after its start. The study also provides evidence that the hospital where patients get their treatment, initial BI readings, and having their treatment extended significantly affected treatment compliance. In addition to age of the patient, these same variables were also associated with treatment default. While most of these findings only corroborate what is already known from other similar studies about the determinants of treatment adherence in leprosy

Table 2. Rates of treatment completion and comparison of treatment completion patterns for each level of exposure of interest.

Exposure variable	Number (%) of Treatment Completers	Person-time (100 person-months)	Rate of treatment completion (per 100 person-months) (95% CI)	p-value of logrank test
Hospital				<0.01
A	155 (65.1)	27.37	5.66 (4.84–6.63)	
B	53 (53.5)	16.21	3.27 (2.50–4.28)	
C	382 (54.8)	79.29	4.82 (4.36–5.33)	
Age Group				0.85
15–29	187 (52.2)	40.62	4.60 (3.99–5.31)	
30–44	232 (60.1)	47.55	4.88 (4.29–5.55)	
45+	171 (59.0)	34.69	4.93 (4.24–5.73)	
Sex of patient				<0.01
Male	428 (55.7)	92.44	4.63 (4.21–5.09)	
Female	162 (61.1)	30.42	5.33 (4.57–6.21)	
Place of residence				0.31
Within Metro Manila	372 (58.8)	75.55	4.92 (4.45–5.45)	
Outside Metro Manila	218 (54.4)	47.29	4.61 (4.04–5.26)	
Initial Bacteria Index Value				<0.01
0	96 (69.1)	15.94	6.02 (4.93–7.35)	
1–3	241 (60.9)	43.47	5.54 (4.89–6.29)	
4-6+	205 (52.4)	50.24	4.08 (3.56–4.68)	
Missing	48 (44.4)	13.22	3.63 (2.74–4.82)	
Treatment Extension				<0.01
No treatment extension	457 (53.3)	80.93	5.65 (5.15–6.19)	
Yes, treatment extended	133 (75.1)	41.93	3.17 (2.68–3.76)	

Table 3. Association of hospital, age category, sex address, initial BI category, and treatment extension with treatment completion.

	Crude Rate Ratio (95% CI)	p-value	Adjusted[a] Hazard Ratio (n = 926) (95% CI)	p-value
Hospital				
A	1 (baseline)		1 (baseline)	
B	0.58 (0.42–0.79)	<0.01	0.61 (0.34–1.08)	0.09
C	0.85 (0.71–1.03)	0.09	0.72 (0.59–0.87)	<0.01
Age Group				
15–29	1 (baseline)		1 (baseline)	
30–44	1.06 (0.87–1.29)	0.55	1.00[b] (0.99–1.00)	0.24
45+	1.07 (0.87–1.32)	0.52		
Sex				
Male	1 (baseline)		1 (baseline)	
Female	1.15 (0.96–1.38)	0.13	0.98 (0.80–1.19)	0.83
Place of residence				
Within Metro Manila	1 (baseline)		1 (baseline)	
Outside Metro Manila	0.94 (0.79–1.11)	0.44	0.94 (0.79–1.12)	0.51
Initial BI				
0	1 (baseline)		1 (baseline)	
1–3	0.92 (0.73–1.17)	0.50	0.93[b] (0.89–0.98)	<0.01
4-6+	0.68 (0.53–0.86)	<0.01		
Treatment extension				
Not extended	1 (baseline)		1 (baseline)	
Extended	0.56 (0.46–0.68)	<0.01	0.02 (0.01–0.04)	<0.01

[a] Adjusted for other variables listed in the table.
[b] Common linear effect.

[1, 5, 11, 12], the findings of our study provide quantitative empirical evidence that underscores the need to re-evaluate the current clinical management of multibacillary leprosy patients [9, 27].

It has been previously documented that there are variations in how hospitals diagnose, manage, and treat the multibacillary leprosy patients, despite the guidelines from the WHO and the Philippine Department of Health [9]. This study corroborates and provides quantitative evidence that such variations result to differences in treatment adherence and defaulting patterns. Rates of treatment completion are highest, while rates of treatment default are lowest among patients of Hospital A. The opposite can be said about Hospital B, however. These findings support the need to assess the effectiveness of the different management practices of leprosy patients, as well as to re-visit clinical practice guidelines in managing multibacillary leprosy patients to encourage, if not ensure, good treatment adherence.

The duration of treatment for multibacillary leprosy patients is sometimes extended by their attending physicians when the latter believe

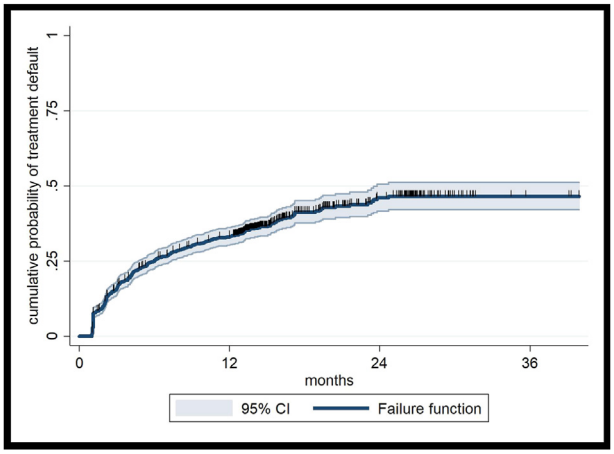

Figure 2. Treatment default pattern of the cohort (n = 1,034).

that reduction in BI levels after 12 months of treatment is insufficient (i.e., 'persisters'), or that relapse is highly likely [9, 10]. This practice of extending treatment beyond 12 months is based on the guidelines of the Northern Territories of Australia [10] and the United States [27], which suggest that treatment duration be extended up to 24 months to ensure that 'persisters' and relapses are minimized. In this study, physicians in Hospitals B and C were more likely to extend the duration of treatment of their multibacillary leprosy patients compared to doctors in Hospital A. This is despite the most recent treatment guidelines of the WHO which prescribes that MDT should only be taken for 12 months [10]. Currently, there is conflicting evidence on the supposed reduction in the risk of relapse as a result of extending MDT to more than the prescribed 12 months duration [27, 28, 29, 30, 31, 32]. However, there is evidence that the incidence, severity, and duration of leprosy reactions are decreased by prolonging the duration of MDT to two years [33]. On the other hand, it is also worth considering that extending the duration of treatment would entail more MDT doses per patient. Given that the supply of MDT is limited, especially in low-income settings, extending the duration of treatment of many patients might lead to MDT shortage. MDT shortage has been frequently mentioned to adversely affect treatment adherence [1, 12]. Nevertheless, these controversies in treatment duration demonstrate the need for studies that look at costs and benefits of treatment extension vis-à-vis the risk of relapse, reactions, and/or being a 'persister'. Such studies are essential to make definite recommendations on how multibacillary leprosy patients, especially those with high BI, should be managed after completing the prescribed 12 months of MDT [9, 27].

The prevention of treatment default can be approached from multiple perspectives, including facility-based efforts to encourage treatment adherence. Healthcare providers at Hospital A send periodic Short Messaging Service (SMS) to remind their patients to seek treatment [9]. This could partly explain why the hospital had the lowest rate of treatment default and the highest rate of treatment completion. The use of SMS to improve treatment adherence has been found to be effective among tuberculosis patients [34], but similar studies among leprosy patients are absent. Due to disruptions brought about by the COVID-19 pandemic, we further anticipate a greater role

Table 4. Rates of default and results of log-rank test for each exposure stratum (n = 1,034).

Exposure variables	Number (%) of Defaulters	Person-time (100 person-months)	Rate of treatment default (95% CI)	p-value of logrank test
Hospital				0.37
A	79 (33.2)	27.37	2.89 (2.32–3.60)	
B	41 (41.4)	16.21	2.53 (1.86–3.44)	
C	263 (37.7)	79.29	3.32 (2.94–3.74)	
Age Group				0.21
15–29	143 (39.9)	40.62	3.52 (2.99–4.15)	
30–44	133 (34.5)	47.55	2.80 (2.36–3.32)	
45+	107 (36.9)	34.69	3.08 (2.55–3.73)	
Sex				0.53
Male	291 (37.8)	92.44	3.15 (2.81–3.53)	
Female	92 (34,7)	30.42	3.02 (2.47–3.71)	
Place of residence				0.50
Within Metro Manila	229 (36.2)	75.57	3.03 (2.66–3.45)	
Outside Metro Manila	154 (38.4)	47.29	3.26 (2.78–3.81)	
Initial Bacterial Index Value				0.14
0	37 (26.6)	15.94	2.32 (1.68–3.20)	
1–3	141 (35.6)	43.47	3.24 (2.75–3.83)	
4-6+	151 (38.6)	50.24	3.01 (2.56–3.53)	
Missing	54 (50.0)	13.22	4.09 (3.13–5.33)	
Treatment extension				<0.01
No treatment extension	352 (41.1)	80.93	4.35 (3.92–4.83)	
Yes, treatment was extended	31 (17.5)	41.93	0.74 (0.52–1.05)	

of e-health interventions in improving medication adherence [35]. However, such efforts are encumbered by the reluctance of some patients to provide accurate contact details to health providers which prevent the latter from sending reminders to patients about their clinic visit schedules [9]. In the end, improving health worker-patient relationship, family/community involvement, more effective patient counseling, patient information, education and communication, and addressing stigma can all be effective strategies to improve treatment adherence [6, 36].

A strength of our study is the use of a cohort design, with data from more than 1,000 patients and 12,000 person-months of follow-up, which allowed us to quantify, with relatively precise confidence intervals, the extent of and the correlates of treatment adherence [37]. We also considered treatment completion and treatment default as separate

Table 5. Association of hospital, age category, sex, address, initial BI category, and treatment extension, with treatment default.

	Crude rate ratio		0–6 mos follow-up (n = 902)		>6 mos follow-up (n = 677)	
	Crude rate ratio (95% CI)	p-value	Adjusted[a] Hazard Ratio (95% CI)	p-value	Adjusted[b] Hazard Ratio (95% CI)	p- value
Hospital						
A	1 (baseline)		1 (baseline)		1 (baseline)	
B	0.88 (0.60–1.28)	0.49	(excluded)		2.80 (1.08–7.30)	0.04
C	1.15 (0.89–1.48)	0.28	1.02 (0.75–1.38)	0.91	1.56 (0.94–2.58	0.08
Age Group						
15–29	1 (baseline)		1 (baseline)		1 (baseline)	
30–44	0.79 (0.63–1.01)	0.06	0.72 (0.53–0.99)	0.04	1.00[c] (0.98–1.01)	0.79
45+	0.88 (0.68–1.13)	0.30	0.94 (0.68–1.30)	0.71		
Sex						
Male	1 (baseline)		1 (baseline)		1 (baseline)	
Female	0.96 (0.76–1.21)	0.74	0.90 (0.66–1.23)	0.52	0.84 (0.52–1.35)	0.46
Address						
Within Metro Manila	1 (baseline)		1 (baseline)		1 (baseline)	
Outside Metro Manila	1.08 (0.88–1.32)	0.49	1.02 (0.78–1.34)	0.89	0.94 (0.63–1.40)	0.78
Initial BI						
0.00	1 (baseline)		1 (baseline)		1 (baseline)	
0.01–3.99	1.40 (0.97–2.00)	0.07	1.02[c] (0.95–1.10)	0.57	1.15[c] (1.03–1.29)	0.01
4.00+	1.30 (0.90–1.86)	0.16				
Treatment extension						
Not extended	1 (baseline)		1 (baseline)		1 (baseline)	
Extended	0.17 (0.12–0.25)	<0.01	(excluded)		0.19 (0.10–0.36)	<0.01

[a] Adjusted for Hospital (but excluding Hospital B), Age Group, Sex, Address, and Initial BI.
[b] Adjusted for Hospital, Age Group, Sex, Address, Initial BI, and Treatment Extension.
[c] Common linear effect.

outcomes because we wanted to identify possible points of intervention to encourage treatment completion and prevent treatment default; two outcomes which may not necessarily measure the same facet of treatment adherence.

Our study has several limitations. Substantial missing data on subsequent BI readings, as well as lack of data on the number of patients seen by each hospital per year, implies that the state of record-keeping is poor. As a result, we cannot rule out selection bias as a result of including only available records in the analysis. Furthermore, around 10% of respondents were not included in the regression analyses due to missing data on initial BI. This may have also resulted to selection bias if absence of data on BI is related to either treatment completion or defaulting. This limitation highlights the need to improve patient-record keeping and if necessary, re-train healthcare providers. In addition to selection bias, misclassification could also be a problem in our study. Some patients failed to notify the hospital when they transferred to other health facility, and as a result, these patients are erroneously classified as 'defaulters' by the hospital. As a result, our study also classified these patients as 'defaulters', when in fact, they should be classified as 'transferees'. Therefore, the number of those who dropped out from treatment may be overestimated, while the number of those who left may be artificially low. Since it is impossible to ascertain the true treatment status of some patients (i.e., whether they really defaulted or just went to other clinics), the effect of this misclassification on the results of the study cannot be ascertained. More importantly, these misclassified patients artificially inflate the prevalence of leprosy in the country because they are counted twice. To address this problem, we recommend that patients should be informed early about proper procedures to take in case they need to transfer to other health facilities. Doing this will hopefully reduce undocumented transfers and improve the accuracy of leprosy statistics in the Philippines. A centralized registry of leprosy patients that is accessible throughout the country can also help address this problem. Lastly, our study may also have residual confounding of the results as data on many of the variables associated with treatment adherence (e.g., socioeconomic status, education, occurrence of adverse drug reactions, erythema nodosum leprosum, and leprosy reactions, etc.) were not collected. Thus, the effect of these variables on the outcomes were not controlled for in the regression analysis.

5. Conclusions

Adherence to MDT among newly diagnosed multibacillary leprosy patients in Metro Manila was low with less than 60% completing treatment and almost 40% defaulting treatment. While many patients complete treatment within the prescribed 12-month period, treatment duration was extended for some because healthcare providers think that the prescribed treatment duration was inadequate to cure the patient or to prevent reactions and relapse. However, this practice of extending treatment might contribute to drug shortages especially in resource-poor settings. Many patients who leave treatment do so within a few months after they start treatment. After adjusting for confounders, there was a strong evidence that significant variations exist in the way clinicians in different hospitals manage their patients. Treatment completion and default rates of patients varied according to initial BI readings, and whether the duration of treatment of a patient was extended by the doctor. Hospitals, where health providers reminded patients through electronic messaging, about their clinic visit schedules, tended to have patients who continue treatment and had significantly lower rates of treatment default compared to patients of hospitals who do not adopt this practice. The results suggest that this practice could be adopted to promote better treatment adherence, like telemedicine which is widely used during the COVID-19 pandemic. In addition, improving doctor-patient relationship, more effective counselling, and IEC about the disease, which also address stigma, are interventions that may improve treatment adherence. As part of improving counselling, it is important to emphasize to patients that they should not stop treatment even if their symptoms improve. The leprosy control program should be able to manage continuity of patient care by coming up with a centralized database of patients and improving the patient referral system between treatment facilities. Protocols for transferring to other treatment facilities should be emphasized to patients at the start of treatment. Future studies can build on our research by doing a prospective cohort study that would address the weaknesses of our study including possible selection bias, residual confounding, and limited generalizability. Future studies could also investigate the management of multibacillary leprosy patients after 12 months of MDT, especially those who still have high BI, to come up with clear recommendations on their duration of treatment and how they should be managed.

6. Other information

The results of this study have been presented orally in the 20th International Leprosy Congress held at Manila, Philippines on September 10–13, 2019.

Declarations

Author contribution statement

Veincent Christian F. Pepito: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Rae Erica D. Samontina: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Sarah Jane A. Abdon and David Norman L. Fuentes: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

Ofelia P. Saniel: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Arianna Maever L. Amit: Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

The authors do not have permission to share data.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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