Results from two cohort studies in Central Africa show that clearance of Wuchereria bancrofti infection after repeated rounds of mass drug administration with albendazole alone is closely linked to individual adherence

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Key point: Longitudinal analysis of data from two community trials of mass drug administration with semi-annual albendazole on lymphatic filariasis demonstrated a clear dose-response treatment effect at individual level that underlines the importance of adherence for LF elimination programs.
Abstract.

Background. Two community trials conducted from 2012 to 2018 in the Republic of Congo and the Democratic Republic of the Congo demonstrated the efficacy of semi-annual mass drug administration (MDA) with albendazole (ALB) alone on lymphatic filariasis (LF). However, a high inter-individual heterogeneity in the clearance of infection was observed.

Methods. We analyzed trial data to assess the effect of individual adherence to ALB MDA on clearance of circulating filarial antigenemia (CFA) and microfilaremia. Community residents were offered a single dose of ALB every 6 months and tested for LF with a rapid test for CFA at baseline and then annually. CFA test results were scored on a semi-quantitative scale. At each round, microfilaremia was assessed in CFA-positives. All CFA-positive subjects for whom at least one follow-up measure was available were included in the analyses. Parametric survival models were used to assess the influence of treatment adherence on LF infection indicators.

Results. Out of 2658 subjects enrolled in the trials, 394 and 129 were eligible for analysis of CFA and microfilaremia clearance, respectively. After adjusting for age, sex and initial CFA score, the predicted mean time for clearing CFA was shorter in persons who had taken 2 doses of ALB per year (3.9 years) than in persons who had taken 1 or 0 dose (4.4 and 5.3 years, \( P < .001 \) for both). A similar pattern was observed for microfilaremia clearance.

Conclusions. These results demonstrate a clear dose-response relationship for the effect of ALB on clearance of CFA and microfilaremia.

Keywords: Albendazole, Lymphatic filariasis, Mass drug administration, Treatment adherence, Parametric survival analysis.
Abbreviations. ALB: albendazole, CFA: circulating filarial antigen, LF: lymphatic filariasis, MDA: mass drug administration, IVM: ivermectin, Mf: microfilariae, SAE: serious adverse events, MFD: microfilarial densities, WHO: World Health Organization, Congo: Republic of the Congo, DRC: Democratic Republic of the Congo, ICT: immunochromatographic card test, FTS: filarial test strip.
Introduction

Lymphatic filariasis (LF) is a mosquito-borne parasitic infection caused mainly by *Wuchereria bancrofti*. The strategy for LF elimination is to interrupt the transmission cycle between humans and vectors. In African countries where onchocerciasis is endemic, programs provide annual mass drug administration (MDA) with ivermectin (IVM) plus albendazole (ALB). Bednets are also often provided to limit mosquito exposure. Treatment with IVM and ALB reduces the density of the larval stages of the parasite (microfilariae, Mf) in the blood. However, MDA has to be repeated for many years because these drugs have a limited efficacy for killing adult worms [1]. In areas where LF is coendemic with loiasis, another filarial infection caused by *Loa loa*, this strategy is dangerous, because IVM can induce serious adverse events (SAE) in people with very high *L. loa* microfilarial densities (MFD) [2]. In these areas, alternative strategies have to be implemented. Previous clinical trials comparing the effects of various drugs on *W. bancrofti* MFD suggested that treatment with ALB alone might reduce MFD, albeit at a slower rate than after combined treatment with IVM and ALB [3–13]. ALB does not induce SAEs in subjects with high *L. loa* MFD [14–16]. In 2012, the World Health Organization (WHO) proposed that MDA with ALB (preferably semi-annual, and combined with integrated vector management) might be used to eliminate LF in areas where loiasis is coendemic [17]. The results of two community trials conducted in the Republic of Congo (Congo) and the Democratic Republic of the Congo (DRC) confirmed that this strategy was effective. In the first site, where baseline circulating filarial antigenemia (CFA) and Mf prevalences were moderate (17.3% and 5.3%, respectively), and treatment adherence was high (83-90%), these indicators decreased to 4.7% and to 0.3%, respectively, after three years of semi-annual MDA with ALB alone [18]. In DRC, where baseline infection prevalences were higher and treatment adherence lower (56-88%), CFA and Mf prevalences decreased from 31.6% to 8.5% and from 12.0% to 0.9%, respectively, after four years of semi-annual MDA with ALB [19]. Although MDA with ALB alone was highly effective at the community level, considerable heterogeneity was observed in parasite clearance at the individual level; some individuals cleared their infections rapidly, while others remained infected after 8 rounds of MDA. In this study, we have reanalyzed data collected from these two community trials.
to assess the effect of individual adherence to ALB treatment on the CFA and *W. bancrofti* microfilaremia clearance rates.

**Methods**

**Study populations**

The design of the two studies has been described elsewhere [18,19]. In Congo, the study was conducted from 2012 to 2015 in Seke-Pembe, a village located in Mabombo Health District (Bouenza division). In DRC, the study site consisted of two contiguous villages (Mbungimi and Misay) located in the Kwilu province, and the trial took place from 2014 to 2018. Study participants were tested for LF infection at baseline and then annually. Both studies were approved by ethics committees and administrative authorities in the respective countries. Adult participants signed an informed consent form. Participants aged < 18 years were enrolled only after verbal assent and if one parent signed a consent form.

A total of 2658 individuals were examined for LF infection at least once during the two studies. The present analysis included all individuals who were CFA-positive at the time of their first test (which was not necessarily performed during the year when the trial started in the site) and who had at least one subsequent examination. Therefore, individuals who had progressed from CFA-negative to positive during the follow-up period and those who were CFA-negative at all time points tested were not included in the analysis.

**Assessment of *W. bancrofti* infection**

Annual parasitological assessments were performed for participants aged ≥ 5 years. LF infections were detected by CFA testing using point-of-care tests. In Congo, testing was done with the BinaxNOW Filariasis immunochromatographic card test (ICT; Alere, Scarborough, ME, USA) in 2012, 2013 and 2014 and with the Filarial Test Strip (FTS; Alere, Scarborough, ME, USA) in 2015. All antigen testing in DRC was performed with FTS. ICT and FTS results were scored semi-
quantitatively (0, 1, 2 or 3 according to the relative intensities of the test and control lines) [18,20]. All CFA-positive individuals were invited to return for blood sampling between 10:00 PM and 1:00 AM for assessment of *W. bancrofti* microfilaremia. MFDs were based on the arithmetic mean of the counts of two 70-microliter thick blood smears and expressed as Mf per milliliter (Mf/mL).

**Drug distribution and assessment of treatment adherence**

CFA-negative individuals were treated with a single tablet of ALB (400 mg) immediately after antigen testing under the direct observation of investigators. Those with positive CFA test results were treated with ALB just after collection of night blood for Mf testing. Residents who had not participated in the parasitological survey were also offered ALB treatment. All treatments were provided under the supervision of a local healthcare worker who was also responsible for conducting a population census before each semi-annual MDA. Every treatment was recorded in a drug treatment register. In addition, during the annual assessment visits, we asked the participants if they had received ALB during the previous MDA campaign, six months earlier. Therefore, for each year of the study, we could determine for each participant whether he/she had taken 2, 1 or 0 ALB tablets.

**Socio-demographics and risk factors for LF**

At inclusion, we collected information about sex and age. At each visit, we also collected, using a standardized 1-page questionnaire, socio-demographic characteristics and habits that are known to be risk factors for LF such as bednet usage and occupation (fishing, hunting, farming and regular sleeping outside of the village in the bush) [21,22].

**Statistical analysis**

The events analyzed are clearance of CFA (the transition from a positive to a negative CFA test during follow-up) and clearance of microfilaremia. We used survival analysis methods [23] to account for the individual follow-up nature of the data. The start date for the survival analysis was the first
visit (index date). Individual observations were censored at the end of the follow-up or at the date of
the event (date of the annual parasitological survey). Each participant’s data were considered for
calculation of cumulative person-years in the survival analysis.

We considered the following covariates for the analysis: sex, initial MFD (categorized in three
categories of similar sample size: 1 to 150, 150 to 300 and > 300 Mf/mL), initial CFA score (from 1
to 3), a history of fishing as an occupation (yes or no) and a history of regularly sleeping in the bush
(yes or no).

We also considered the following time-varying covariates: age (categorized according to interquartile
and median values: 5-17, 18-30, 31-45 and ≥ 46 years old), number of ALB tablets taken during the
previous year (0, 1 or 2), bednets use during the previous night (yes or no), the CFA test used (ICT or
FTS).

Univariate analysis of clearance rates was conducted using Mantel-Haenszel tests. Clearance rates
represents the probability of occurrence of clearance in a specified period of time.

We used a parametric survival models with accelerated failure time [24] to estimate the influence of
time-varying variables on infection clearance (time-to-event)[25]. Several time distributions that do
not require meeting the proportional risk assumption were tested according to Akaike Information
Criterion (AIC). For the survival models, random effects, at both village and household levels, were
assessed using results of likelihood-ratio tests. Results are presented as time ratios with 95%
confidence intervals (95% CI). Time ratios represent time differences to event according to the
reference category. Socio-demographic data, occupation, initial infection intensity (CFA and/or MFD)
and the numbers of ALB tablets taken each year were included in the CFA and microfilaremia
clearance survival models. The type of test (ICT or FTS) was included in the CFA clearance model.
The fitted models used to estimate average times to clear CFA and microfilaremia included all
explanatory variables.

A mixed model with random effect at individual level was used to describe changes in MFD
according to time, treatment history and socio-demographic information. Several transformations
(linear, quadratic, first-order fractional polynomials and second-order fractional polynomials) were
tested for the time variable and selection was made according to AIC. As for CFA clearance analysis, random effects at village and household levels were assessed. Lastly, the significance of relevant interaction terms was assessed (age and sex, age and initial CFA score, age and initial MFD, age and number of ALB treatments taken, sex and initial CFA score, sex and initial MFD, sex and number of ALB treatments taken) for CFA and microfilaria clearance and MFD change analyses. All analyses were performed using STATA v.15.1 software (StatCorps, LP, College Station, TX, USA).

Results

Study participants

Out of the 2658 participants enrolled in the studies, 879 were only tested once; 22 who were CFA-negative at baseline acquired CFA (15 in DRC and 7 in Congo), and 1363 were CFA-negative at baseline and all follow-up times. Thus, observations from 394 participants were available for analysis of CFA clearance for a total of 1369 person-years of follow-up and 203 CFA clearance events. For the microfilaria clearance analysis, 129 subjects had a total of 400 person-years of follow-up with 100 microfilaria-clearance events. The survival data concerning non-time varying variables are summarized in Table 1.

CFA and microfilaria clearance rates

Clearance rates with significance values are presented in Table 2. The probability of CFA clearance was negatively correlated with initial CFA score and the probability of microfilaria clearance was negatively correlated with initial MFD. A history of sleeping regularly in the bush decreased the probability of CFA clearance. CFA clearance was also more likely in the Congo site than in DRC. The probabilities for clearance of CFA for each of the 39 treatment patterns during the 5-year period are included in the supplementary material 1.
Parametric survival multivariate models for the clearance of CFA and microfilaremia

Results from the parametric survival model analyses are presented in Table 3. Log-logistic distribution and log-normal distribution were the best fits for time in the CFA and microfilaremia clearance models, respectively. No interactions between covariates were found. A random effect at village level \((P = .0277)\) was included in the CFA clearance model (Intraclass Correlation Coefficient \(= 7.27\%\)), but this was not significant in the microfilaremia clearance model \((P = .346)\). CFA score at inclusion, frequent sleeping outdoors, and type of CFA test were all significantly associated with CFA clearance. Times to CFA clearance were significantly longer in individuals with higher initial CFA scores. Sleeping outdoors significantly increased the time to CFA clearance. Assessment of the CFA by ICT decreased the observed duration to CFA clearance. Predicted average time for clearing CFA was shorter in those who had taken two doses of ALB per year \((3.9 \text{ years})\) than in those who has taken 1 or 0 dose \((4.4 \text{ and 5.3 years, } P < .001 \text{ for both comparisons})\). Microfilaremia clearance had a similar pattern: individuals who had taken two doses of ALB per year became amicrofilaremic after a mean time of 3.1 years, whereas those who had taken 1 or 0 dose per year needed 3.6 \((P < .001)\) and 5.9 years \((P < .001)\), respectively, to clear their microfilaremia. Time to microfilaremia clearance was also significantly longer in individual with higher initial MFD.

Changes in MFD over time

No transformation of time was required for the model. Neither the village- \((P = .496)\) nor the household-level \((P = .529)\) random effect was significant in the mixed model. Results from the mixed model with no random effect are presented in Table 4. MFD reduction was more rapid when individuals were adherent with MDA. The decrease in MFD was not significantly different in those who had taken 0 or 1 dose of ALB per year. Figure 1 shows predicted changes in MFD according to the number of doses taken per year with time transformation into a fractional polynomial of order 2 (see Supplementary Material 2). All predictions were adjusted for sex, age and initial MFD.

Differences in slopes were highly significant between 0 and 2 doses of ALB \((P = .009)\), between 2 and 1 dose \((P = .004)\), but not significant between 1 and 0 dose \((P = .419)\).
Discussion

The WHO’s provisional recommendation to use semi-annual MDA with ALB alone to control LF in areas where *L. loa* is coendemic was based on thin evidence. The few trials [5,11–13] that had evaluated the effect of a single dose of ALB on LF infection had demonstrated a modest effect of the drug on MFD. In addition, two meta-analyses of the efficacy of a single dose of ALB alone on Mf and CFA prevalences concluded that this treatment would induce only a small to non-existent decrease in these outcomes at 3, 6, or 12 months post-treatment [26,27].

We conducted community trials in two settings to evaluate the impact of semi-annual MDA with ALB on LF [18,19]. However, a major methodological limitation of these trials was that the effect of semi-annual treatment was not directly compared to that of annual treatment or no treatment. Thus, the analyses presented here provide important information regarding the added value of semi-annual ALB treatment vs annual MDA or no treatment on LF infection parameters. Our longitudinal analyses from infected persons clearly demonstrate a dose-response effect for ALB treatment on CFA and on microfilaremia. Our results show that good adherence leads to faster clearance of LF infection in individuals. Both clearances were significantly associated with the number of doses of ALB taken annually, and with initial infection levels. A lower initial CFA score was associated with a higher probability of CFA clearance. Therefore, the knowledge of the individual semi-quantitative results at baseline may be useful to improve planning for LF elimination programs. The use of the ICT test was associated with an increased probability of CFA clearance relative to use of the FTS, and this is likely due to the higher sensitivity of the FTS [28]. Although baseline CFA scores were not associated with more rapid clearance of microfilaremia, higher initial MFD increased the time required for total microfilaremia clearance.

Regarding individuals’ exposure and habits, individuals who sleep regularly outdoors took longer to clear CFA. This was probably due to reinfection, because prior studies have identified sleeping outdoors as a significant risk factor for LF in central Africa [21,22]. However, the use of bednets or a history of fishing were not significantly associated with the clearances. Although the non-use of
bednets has been shown to be a risk factor for LF infection, their use in infected individuals (without MDA) was not effective for clearing infections or for reducing Mf prevalence in the time frames (3 or 4 years) of this study [29]. Data on the relationship between bednet usage and treatment adherence are included in the supplementary material 3. Hunting and agricultural activities were not included in the models, because the numbers of hunters and farmers were small in the study sites, and inclusion of these occupations would have destabilized the models. Individuals were more likely to clear CFA after MDA in Congo than in DRC. This might be due to the fact that therapeutic coverage was higher and more constant and baseline infection prevalence lower, in the Congo site than in DRC which may reduce transmission and, therefore, the probability that re-infection occurs.

The activity of ALB alone for LF has important implications for current protocols that rely heavily on CFA surveys in school-aged children for MDA stopping decisions and post-MDA surveillance. Indeed, since soil-transmitted helminth programs routinely only treat children, using this demographic as a sentinel for MDA stopping decisions may underestimate the level of community-wide transmission because LF will tend to be less prevalent in children, who are more treated than adults.

We elected to use parametric survival models to analyze these data because these models are more flexible and allow longitudinal analyses with time-varying variables (i.e. ALB intake). In addition, they are more informative than non-parametric approaches, because they provide time ratios, enable predictions of mean and median survival times and have more power than semi-parametric models.

Log-logistic distribution for the CFA clearance model and log-normal distribution for the microfilaremia clearance model were the best fits for our data, and they have the advantage of not requiring proportional risk assumptions, unlike conventional Cox survival models.

The presence of bias cannot be excluded. Prevalence bias may be present. However, fewer than 11% of the population (8.5 and 10.4% for the CFA and microfilaremia clearance models, respectively) had taken ALB prior to our study. We believe that this bias, if it exists, would have had very little impact on our results. In addition, participation bias cannot be excluded either: people with a high participation frequency in our study may have different characteristics than non-participants, including adherence with treatment.
We have mentioned that participation rates in MDA decreased over time, probably reflecting a kind of fatigue on the part of some community members [19]. We believe that we have demonstrated through these new analyses that participation rates in MDA programs must be maintained at high levels to accelerate the elimination of LF in individuals and communities. Evidence from this study could be used in social mobilization programs to illustrate the importance of achieving and sustaining high rates of MDA adherence in LF elimination programs.
Acknowledgments. We thank the authorities and residents of the study sites for their active participation in the trials, and the personnel from the Ministries of Health of Congo and DRC for their assistance.

Funding. Initial trials were funded by grant GH5342 from the Bill & Melinda Gates Foundation. No additional funds were required for this study.

Conflicts of interest. The authors declare that they have no competing interests.
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Tables

Table 1. Survival data for time constant variables used in circulating filarial antigenemia (CFA) and microfilaremia survival models.

| Variable            | Person-years | Number of events |
|---------------------|--------------|------------------|

Table 2. Univariate clearance rates for circulating filarial antigenemia (CFA) and microfilaremia.

| Rate Type | Description                  | Value | 95% Confidence Intervals |
|-----------|------------------------------|-------|--------------------------|

Table 3. Results from parametric survival models for CFA (with village as a random effect) and microfilaremia clearance.

| Rate Type | Description                  | Value | 95% Confidence Intervals |
|-----------|------------------------------|-------|--------------------------|

Table 4. Mixed model results for the evolution of Mf density (MFD).

| Rate Type | Description                  | Value | 95% Confidence Intervals |
|-----------|------------------------------|-------|--------------------------|

Figures:

Figure 1. Predictions of Mf densities (MFD) evolution according to time (fractional polynomial of order 2) and adherence with MDA (A: 0 dose per year, B: 1 dose per year; C: 2 doses per year).

Full model and time transformations are available in Supplementary Material 2.
| Variables                  | Categories            | CFA clearance | Microfilaremia clearance |
|----------------------------|-----------------------|---------------|--------------------------|
|                            |                       | PY \(^a\) | Events \(^b\) | PY \(^a\) | Events \(^b\) |
| Sex                        | Male                  | 754        | 112            | 232        | 61          |
|                            | Female                | 615        | 91             | 168        | 39          |
| Age at inclusion           | 5 – 17 years          | 304        | 47             | 87         | 22          |
|                            | 18 – 30 years         | 349        | 48             | 92         | 23          |
|                            | 31 – 45 years         | 402        | 59             | 113        | 24          |
|                            | ≥ 46 years            | 314        | 49             | 108        | 31          |
| CFA score at inclusion     | 1                     | 488        | 128            | 30         | 9           |
|                            | 2                     | 352        | 51             | 91         | 28          |
|                            | 3                     | 529        | 24             | 279        | 63          |
| Bednets use at inclusion   | No                    | 561        | 82             | 138        | 33          |
|                            | Yes                   | 808        | 121            | 262        | 67          |
| Fishing activities at      | No                    | 596        | 100            | 161        | 43          |
| inclusion                  | Yes                   | 699        | 95             | 211        | 52          |
| History of sleep outside   | No                    | 953        | 159            | 248        | 63          |
| at inclusion               | Yes                   | 408        | 44             | 144        | 36          |
| Village                    | Misay (DRC)           | 297        | 39             | 85         | 21          |
|                            | Mbunkimi (DRC)        | 660        | 79             | 199        | 49          |
|                            | Seke Pembe (Congo)    | 412        | 85             | 116        | 30          |
| Study site                 | Bouenza (Congo)       | 957        | 118            | 284        | 70          |
|                            | Kwilu (DRC)           | 412        | 85             | 116        | 30          |
| Initial MFD                | 0 – 150 Mf/mL         | 144        | 44             |            |             |
|                            | 151 – 300 Mf/mL       | 77         | 22             |            |             |
|                            | > 300 Mf/mL           | 179        | 34             |            |             |

Table 1. Survival data for time constant variables used in circulating filarial antigenemia (CFA) and microfilaremia survival models.

\(^a\) Person-years

\(^b\) Number of events.
| Variables | Categories | CFA Clearance rates \(^a\) | 95% CI \(^b\) | P \(^c\) | Microfilaremia Clearance rates \(^a\) | 95% CI \(^b\) | P \(^c\) |
|-----------|------------|----------------|----------|-----|----------------|----------|-----|
|           |            | 14.8           | 12.9 – 17.0 |      | 25.0           | 20.5 – 30.4 |      |
| Sex       | Male       | 14.8           | 12.0 – 18.2 | .989 | 26.3           | 20.4 – 33.8 | .543 |
|           | Female     | 14.8           | 12.3 – 17.9 |      | 23.2           | 17.0 – 31.8 |      |
| Age at inclusion | 5 – 17 years | 15.5 | 11.6 – 20.6 | .859 | 25.3 | 16.6 – 38.4 | .739 |
|           | 18 – 30 years | 13.7 | 10.4 – 18.2 |      | 25.0 | 16.6 – 37.6 |      |
|           | 31 – 45 years | 14.7 | 11.4 – 18.9 |      | 21.2 | 14.2 – 31.7 |      |
|           | ≥ 46 years | 15.6 | 11.8 – 20.6 |      | 28.7 | 20.2 – 40.8 |      |
| CFA score at inclusion | 1 | 26.2 | 22.1 – 31.2 | < .0001 | 30.0 | 15.6 – 57.6 | .184 |
|           | 2 | 14.5 | 11.0 – 19.1 |      | 30.8 | 21.2 – 44.6 |      |
|           | 3 | 4.5 | 3.0 – 6.8 |      | 22.6 | 17.6 – 28.9 |      |
| Bednets use at inclusion | No | 14.6 | 11.8 – 18.1 | .677 | 23.9 | 17.0 – 33.6 | .752 |
|           | Yes | 14.9 | 12.5 – 17.9 |      | 25.6 | 20.1 – 32.5 |      |
| Fishing activity at inclusion | No | 16.8 | 13.8 – 20.4 | .671 | 19.0 | 14.1 – 25.6 | .444 |
|           | Yes | 13.6 | 11.1 – 16.6 |      | 16.2 | 12.4 – 21.3 |      |
| History of sleep outside at inclusion | No | 16.7 | 14.3 – 19.5 | .042 | 26.7 | 19.8 – 36.0 | .696 |
|           | Yes | 10.8 | 8.0 – 14.5 |      | 24.6 | 18.8 – 32.2 |      |
| Village | Misay (DRC) | 13.1 | 9.6 – 18.0 | < .0001 | 24.7 | 16.1 – 37.9 | .859 |
|           | Mbunkimi (DRC) | 12.0 | 9.6 – 14.9 |      | 24.6 | 18.6 – 32.6 |      |
|           | Seke Pembe (Congo) | 20.6 | 16.7 – 25.5 |      | 25.9 | 18.1 – 37.0 |      |
| Study site | Bouenza (Congo) | 12.3 | 10.3 – 14.8 | < .001 | 24.6 | 19.5 – 31.1 | .826 |
|           | Kwilu (DRC) | 20.6 | 16.7 – 25.5 |      | 25.9 | 18.1 – 37.0 |      |
| Initial MFD | 1 – 150 Mf/mL |           |          |      | 30.6 | 22.7 – 41.0 | .036 |
|           | 151 – 300 Mf/mL |           |          |      | 28.6 | 18.8 – 43.4 |      |
|           | > 300 Mf/mL |           |          |      | 19.0 | 13.6 – 26.6 |      |

Table 2. Univariate clearance rates for circulating filarial antigenemia (CFA) and microfilaremia.

\(^a\) Calculated for 100 PY.

\(^b\) 95% confidence intervals.

\(^c\) P is calculated from significance tests using Mantel-Haenszel method based on stratified rate ratios.
| Variables          | Categories | CFA clearance | Microfilaremia clearance |
|--------------------|------------|---------------|--------------------------|
|                    |            | TR \(^a\)    | 95% CI \(^b\) | P    | TR \(^a\) | 95% CI \(^b\) | P    |
| Sex                | Female     | Ref.          | Ref.          |      | Ref.          | Ref.          |      |
|                    | Male       | 1.01          | 0.96–1.06     | .718 | 0.94          | 0.84–1.05     | .281 |
| Age                | 5 – 17 years | Ref.          | Ref.          |      | Ref.          | Ref.          |      |
|                    | 18 – 30 years | 1.00          | 0.93–1.07     | .910 | 1.02          | 0.87–1.20     | .769 |
|                    | 31 – 45 years | 1.02          | 0.95–1.08     | .515 | 1.15          | 0.98–1.34     | .082 |
|                    | ≥ 46 years | 1.00          | 0.93–1.07     | .992 | 1.03          | 0.89–1.20     | .644 |
| Initial CFA score  | 1          | Ref.          | Ref.          |      | Ref.          | Ref.          |      |
|                    | 2          | 1.14          | 1.08–1.20     | < .001 | 0.91         | 0.74–1.11     | .357 |
|                    | 3          | 1.40          | 1.31–1.51     | < .001 | 1.00         | 0.83–1.21     | .982 |
| Annual treatment   | 0 dose    | 1.35          | 1.26–1.45     | < .001 | 1.82         | 1.46–2.27     | < .001 |
|                    | 1 dose    | 1.12          | 1.06–1.19     | < .001 | 1.18         | 1.04–1.34     | .008 |
|                    | 2 doses   | Ref.          | Ref.          |      | Ref.          | Ref.          |      |
| Bednets            | No        | Ref.          | Ref.          |      | Ref.          | Ref.          |      |
|                    | Yes       | 0.98          | 0.94–1.03     | .515 | 0.94         | 0.84–1.04     | .243 |
| Fishing            | No        | Ref.          | Ref.          |      | Ref.          | Ref.          |      |
|                    | Yes       | 0.97          | 0.92–1.02     | .280 | 1.06         | 0.95–1.18     | .305 |
| Sleep outside      | No        | Ref.          | Ref.          |      | Ref.          | Ref.          |      |
|                    | Yes       | 1.09          | 1.03–1.16     | .002 | 1.05         | 0.94–1.18     | .397 |
| Test used          | FTS       | Ref.          |               |      |               |               |      |
|                    | ICT       | 0.76          | 0.69–0.85     | < .001 |               |               |      |
| Initial MFD        | 1 – 150 Mf/mL | Ref.          |               |      |               |               |      |
|                    | 151 – 300 Mf/mL | 1.04          | 0.92–1.19     | .514 |               |               |      |
|                    | > 300 Mf/mL | 1.28          | 1.14–1.43     | < .001 |               |               |      |

Table 3. Results from parametric survival models for CFA (with village as a random effect) and microfilaremia clearance.

\(^a\) Adjusted time ratio

\(^b\) 95% confidence intervals.
| Variables          | Categories                  | Adjusted coefficients | 95% CI $^a$   | $P$  |
|--------------------|-----------------------------|-----------------------|---------------|------|
| Sex                | Female                      | Ref.                  | -             | -    |
|                    | Male                        | -26.6                 | -131.2 – 77.9 | .618 |
| Age                | 5 – 17 years                | Ref.                  | -             | -    |
|                    | 18 – 30 years               | -93.1                 | -236.6 – 50.4 | .203 |
|                    | 31 – 45 years               | 35.3                  | -103.6 – 174.1| .619 |
|                    | ≥ 46 years                  | -59.6                 | -196.8 – 77.5 | .394 |
| Initial CFA score  | 1                           | Ref.                  | -             | -    |
|                    | 2                           | -37.8                 | -250.9 – 175.4| .728 |
|                    | 3                           | 52.6                  | -156.8 – 262.0| .622 |
| Initial MFD        | 1 – 200 Mf/mL               | Ref.                  | -             | -    |
|                    | > 200 Mf/mL                 | 221.3                 | 124.3 – 318.3 | < .001|
| Bednets            | No                          | Ref.                  | -             | -    |
|                    | Yes                         | 29.9                  | -61.9 – 121.8 | .523 |
| Fishing            | No                          | Ref.                  | -             | -    |
|                    | Yes                         | -18.5                 | -133.9 – 96.9 | .753 |
| Sleep outside      | No                          | Ref.                  | -             | -    |
|                    | Yes                         | -21.0                 | -138.5 – 96.5 | .753 |
| Annual treatment   | 0 dose                      | Ref.                  | -             | -    |
|                    | 1 dose                      | 177.8                 | -472.3 – 828.0| .592 |
|                    | 2 doses                     | 416.6                 | -217.3 – 1050.5| .198 |
| Time               | Continuous                  | -22.0                 | -174.6 – 130.5| .777 |
| Annual treatment   | 0 dose                      | Ref.                  | -             | -    |
|                    | 1 dose                      | -68.6                 | -234.9 – 97.7 | .419 |
|                    | 2 doses                     | -210.9               | -369.3 – -52.44| .009 |

Table 4. Mixed model results for the evolution of Mf density (MFD).

$^a$ 95% confidence intervals.
