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The Effect of Compliance on the Impact of Mass Drug Administration for Elimination of Lymphatic Filariasis in Egypt

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Abstract. We studied effects of compliance on the impact of mass drug administration (MDA) with diethylcarbamazine and albendazole for lymphatic filariasis (LF) in an Egyptian village. Baseline microfilaremia (mf) and filarial antigenemia rates were 11.5% and 19.0%, respectively. The MDA compliance rates were excellent (> 85%). However, individual compliance was highly variable; 7.4% of those surveyed after five rounds of MDA denied having ever taken the medications and 52.4% reported that they had taken all five doses. The mf and antigenemia rates were 0.2% and 2.7% in those who reported five doses of MDA and 8.3% and 13.8% in those who reported zero doses. There was no significant difference in residual infection rates among those who had taken two or more doses. These results underscore the importance of compliance for LF elimination programs based on MDA and suggest that two ingested doses of MDA are as effective as five doses for reducing filariasis infection rates.

INTRODUCTION

The Global Program to Eliminate Lymphatic Filariasis (GPELF) has the ambitious goal of eliminating LF in all disease-endemic areas by the year 2020.¹ The GPELF aims to permanently interrupt transmission of LF with a program that is largely based on mass drug administration (MDA) with antifilarial medications that reduce microfilaremia (mf) rates in communities to levels below those needed for sustained transmission by mosquitoes. The MDA programs were initiated in several countries in 2000. The global program rapidly expanded, and more than 380 million people in 42 countries received MDA for LF in 2005 (the last year with reported numbers).² With a stated goal of providing MDA to some 1.3 billion people by the year 2020, this program is easily the largest infectious disease intervention that has ever been attempted based on MDA.

Filarial worms have long life spans, and antifilarial medications do not work unless they are ingested. Mathematical models that simulate LF transmission^{3,4} and GPELF guidelines emphasize the importance of achieving high MDA coverage rates.^{5,6} Reported MDA coverage rates vary,^{7–9} and compliance rates (percentage of people who report having taken the medications) are sometimes much lower than coverage rates (percentage of people who received the medications) reported by public health authorities.¹⁰ Compliance rates have decreased after several rounds of MDA in some areas¹¹ but have increased in others.^{8,12} A number of factors contribute to MDA noncompliance, including ignorance or indifference in the target population regarding LF, fear of adverse events from treatment, distrust of government programs, and failure to receive the medications.^{8,10,13}

Bancroftian filariasis has been endemic in Egypt for centuries.¹⁴ A 1993 publication estimated that 250,000 people were infected and 2.5 million at risk for infection at that time in eight governorates, mostly in the Nile river delta region

(Lower Egypt) and in Giza.¹⁵ The Egyptian Ministry of Health and Population (MOHP) initiated a national program to eliminate LF in 2000.¹⁶ This was one of the first national LF elimination programs based on the GPELF strategy. The program was planned and coordinated by MOHP with technical assistance from the academic community and the World Health Organization. Directly observed MDA (DO-MDA) was conducted in all known filariasis-endemic localities in the country with annual doses of diethylcarbamazine (DEC, 6 mg/kg) with albendazole (400 mg). Local health teams from MOHP primary health care units distributed medications on a house-to-house basis, with directly observed ingestion of tablets when possible. Teams visited houses a second time to reach household members who were absent on the first visit, and separate teams were based in primary health care units to provide MDA to people who were missed during home visits by the regular MDA distribution teams. The program was supported by a broad-based publicity campaign, and excellent MDA coverage rates were achieved.^{17,18} We have previously reported results of a prospective study of the impact of five rounds of MDA on filariasis endemicity and transmission in sentinel Egyptian villages.¹⁹ The present report addresses the critical issue of the effects of varying levels of compliance on the impact of MDA. Our results underscore the importance of compliance for LF elimination programs based on MDA and suggest that two ingested doses of MDA are as effective as five ingested doses for reducing filarial infection rates.

METHODS

Study design. The study was conducted in two adjacent sectors of Azizia village (Kafr El Bahary and Kafr El Qebly), which is located in Giza Governorate approximately 40 km southwest of Cairo. This village had the highest known mf prevalence in Egypt just prior to initiation of the national filariasis elimination program. The two village sectors were mapped, and houses were numbered with painted numbers. We conducted a cross-sectional survey for *W. bancrofti* infection (see below) just prior to the first round of MDA with repeated surveys 6–8 months after each round of MDA. The total population of the study area was approximately 10,000. Each survey studied approximately 1,000 people older than

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five years of age in 200 households that were randomly selected each year using SPSS software (SPSS Inc., Chicago, IL). Survey teams comprised of a physician, a technician, and a local health worker visited houses in the early evening. Field personnel recorded demographic and MDA compliance information (for post-MDA surveys) on preprinted forms. Parents provided treatment histories for their children.

Compliance rates were estimated by dividing the number of study participants in survey households who reported having taken DEC and albendazole in the previous round of MDA by the total number of study participants who lived in these houses.

Tests for *Wuchereria bancrofti* infection. Finger prick blood samples were collected for detection of *W. bancrofti* antigenemia (circulating filarial antigenemia [CFA]) with rapid-format card tests.^{20,21} Immunochromatographic card tests for filariasis (AMRAD, French's Forest, New South Wales, Australia) were used for the first three surveys and Filariasis Now® cards (Binax, Portland, ME) were used for surveys after MDA rounds 3–5. Subjects with positive filariasis antigen test results were tested for mf by membrane filtration of 1 mL of venous blood collected between 9:00 PM and 1:00 AM as previously described.²² The mf prevalence rate was defined as the number of people with mf divided by the number of people tested for filarial antigenemia. This rate slightly underestimates the true mf prevalence rate because the sensitivity of the antigen card test in mf carriers (as detected by membrane filter) is approximately 95%.^{20,23}

Consent procedures and ethical review. Survey teams explained the study to study participants and obtained informed consent from all adult participants. Child participation required consent of at least one parent and the assent of the child. The study protocol was reviewed and approved by institutional review boards at Washington University School of Medicine (St. Louis, MO) and at Ain Shams University (Cairo, Egypt). The Egyptian Ministry of Health and Population also reviewed and approved the study.

Statistical methods. Data entry was performed with EpiInfo software (version 6)²⁴ with field limits and double data entry. We performed statistical analyses using SAS 9.1 for Windows (SAS, Cary, NC) procedures PROC GLIMMIX to adjust for correlation within household (random effect) and to fit mixed logistic regression models. Age and sex of individual subjects were included as fixed effects in the models to test their significance. Because data were collected each year for six years, linear contrasts were used to increase power to compare infection and MDA compliance at different times for different numbers of MDA doses taken.

RESULTS

Baseline filarial infection prevalence rates. Baseline mf and filarial antigenemia rates were 11.5% and 19.0%, respectively. Baseline filarial infection rates are shown by age and sex in Figure 1. The shapes of the histograms are similar for both parameters, although CFA rates were consistently higher than mf rates, as expected. Infection rates varied significantly by age ($P < 0.001$ for both mf and CFA) with peak prevalence rates between the ages of 16 and 35 years. This difference was mostly caused by decreased rates in young children, and there was no significant age effect when the youngest age group was excluded from the analysis. Although

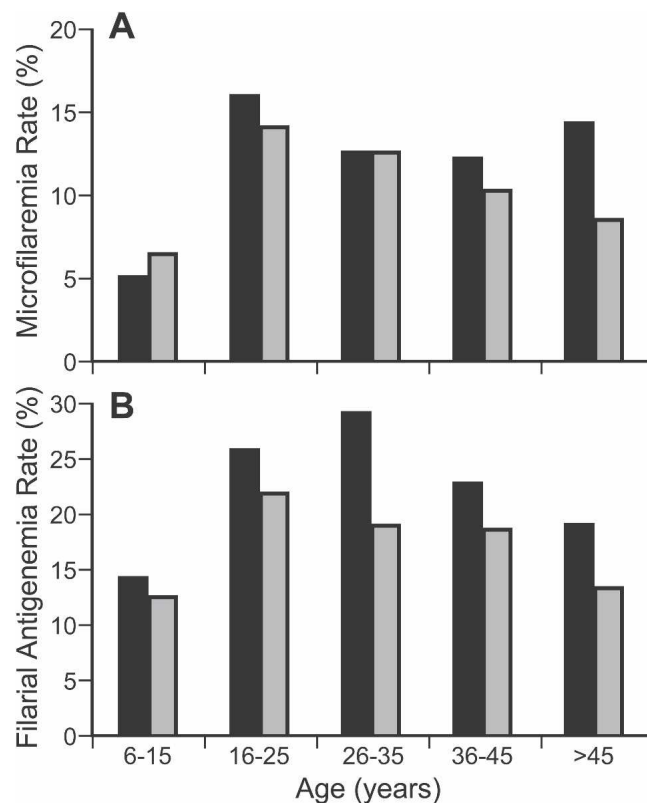


FIGURE 1. Baseline (before mass drug administration), age-specific prevalence rates for **A**, microfilariaemia and **B**, filarial antigenemia in males (black bars) and females (gray bars) in Egypt.

infection rates tended to be higher in males than in females, these differences were not statistically significant ($P = 0.30$ for mf and $P = 0.08$ for CFA).

Compliance with MDA. Overall compliance rates for the surveyed population were 86.7%, 95.5%, 90.1%, and 88.8% for MDA rounds 1–4. Thus, there was no significant decrease in reported compliance rates over time. Compliance rates did not vary significantly by age group or sex. Table 1 shows the cumulative number of doses of annual MDA that people reported having taken after each round of MDA. Note that 52% of the people surveyed after MDA round 5 reported having taken all five doses. The percentages of subjects who reported having taken only zero or one dose of MDA did not decrease significantly after MDA round 3.

Relationships between the number of MDA doses taken and residual infection rates. Figure 2 shows relationships between reported MDA compliance and mf and CFA rates after MDA round 5. People who reported that they had taken no MDA had a higher mf rate than those who reported that they had taken one dose of MDA ($P = 0.002$); CFA rates were not significantly different in these two groups. The mf and CFA rates were similar in those who reported that they had taken two or more annual doses of MDA, and these rates were significantly lower than those in people who reported that they had taken zero or one dose of MDA ($P = 0.006$ for mf and $P < 0.0001$ for CFA). Reductions in infection rates after MDA were not significantly different by age group or sex.

Relative infection rates after MDA. Table 2 shows infection rates relative to baseline rates according to the reported cumulative number of annual MDA doses taken when people

TABLE 1

Reported compliance with mass drug administration (MDA) for lymphatic filariasis in the study area in Egypt*

| MDA Round | Cumulative no. (%) of annual MDA doses ingested | | | | | | Total |
|-----------|---|-------------|-------------|-------------|-------------|-------------|-------|
| | 0 | 1 | 2 | 3 | 4 | 5 | |
| 1 | 178 (17.59) | 834 (82.41) | | | | | 1,012 |
| 2 | 44 (4.29) | 153 (14.93) | 828 (80.78) | | | | 1,025 |
| 3 | 53 (5.25) | 84 (8.33) | 165 (16.35) | 707 (70.07) | | | 1,009 |
| 4 | 80 (7.17) | 124 (11.12) | 271 (24.30) | 137 (12.29) | 503 (45.11) | | 1,115 |
| 5 | 79 (7.42) | 57 (5.36) | 100 (9.40) | 162 (15.23) | 109 (10.24) | 557 (52.35) | 1,064 |

* Values are the no. of people (%) who reported having taken different numbers of doses of MDA in interviews conducted 6–8 months after each round of MDA.

were interviewed after MDA round 5. Filarial antigenemia and mf rates in people who reported zero doses of MDA were lower than baseline rates, but these decreases were not statistically significant ($P = 0.59$ and 0.32 , respectively). Antigenemia and mf rates in those who reported taking one dose of MDA were significantly lower than baseline rates ($P = 0.02$ and $P = 0.03$, respectively). Antigenemia and mf rates in those who reported taking two or more doses of MDA were significantly lower than baseline rates ($P = 0.01$ and $P = 0.005$, respectively). Relative mf rates were lower than relative CFA rates for people with the same MDA compliance histories.

DISCUSSION

The purpose of this study was to examine the effect of compliance on the impact of MDA on filariasis infection rates

in a filariasis-endemic Egyptian community. The MDA compliance rates were excellent in this community and consistent with generally high coverage rates reported by the Egyptian MOHP.^{17,18} We did not observe a decrease in compliance rates in later years of the study.

Two major factors contributed to high MDA compliance rates reported in this study. The Egyptian government’s social mobilization efforts emphasized the importance of LF as a disabling disease that could be eliminated by a time-limited, focused effort.¹⁶ Education programs had simple messages that were delivered with posters in villages, with announcements in places of worship, and with skits and advertisements on television and radio. Elimination of LF was also promoted in schools. Children were given special comic books and other educational materials regarding LF elimination at school,²⁵ and children may have been important advocates for the LF elimination program in their homes and villages. It is important to note that health education messages were delivered prior to the first round of MDA and reinforced just prior to each of the subsequent rounds.

The method of MDA delivery (DO-MDA) was critically important for ensuring high compliance in our study area and more generally in Egypt. The DO-MDA was distributed by local health teams comprised of physicians, nurses, and other workers from primary health care units; trusted, local professional teams took the time to deliver the medications to each house with directly observed ingestion of medications in most cases. Compliance rates would not have been as high or as sustained if strangers from the provincial capital had arrived in vans once per year to drop off cartons of tablets in village markets. Other investigators have emphasized the importance of community involvement for achieving high MDA compliance rates in filariasis elimination programs.^{26–28} We believe that the GPELF should consider revising program manager guidelines to emphasize house-to-house DO-MDA as the preferred method for distribution of MDA in LF elimi-

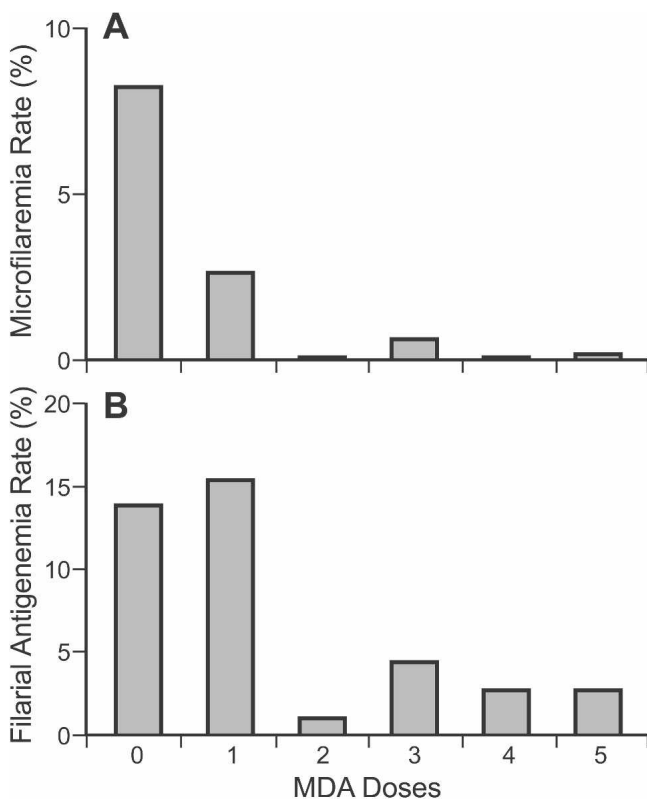


FIGURE 2. **A**, Microfilaria and **B**, filarial antigenemia rates according to compliance with mass drug administration (MDA) as reported in interviews conducted 6–8 months after the last round of MDA in Egypt.

TABLE 2

Residual filarial infection rates relative to baseline rates according to the reported total number of mass drug administration (MDA) doses ingested in Egypt*

| Total MDA doses reported | No. | Filarial antigenemia rate relative to baseline (%) | Microfilaria rate relative to baseline (%) |
|--------------------------|-----|--|--|
| 0 | 79 | 65.9 | 65.4 |
| 1 | 57 | 81.0 | 15.1 |
| 2 | 100 | 5.3 | 0 |
| 3 | 162 | 22.5 | 5.3 |
| 4 | 109 | 14.3 | 0 |
| 5 | 557 | 14.0 | 1.5 |

* Compliance with MDA was based on interviews conducted 6–8 months after the fifth round of MDA.

nation programs. Although DO-MDA requires more resources than other distribution methods, it should pay for itself if it can improve compliance rates enough to reduce the number of MDA rounds required for LF elimination.

Our results confirm that MDA with DEC and albendazole can be highly effective for reducing LF infection rates in communities. Although GPELF guidelines call for four to six rounds of MDA with high coverage for LF elimination programs,^{5,6} there is some uncertainty in the LF community regarding the number of rounds of MDA that are actually needed to achieve LF elimination (reduction of infection rates to levels below those required for sustained transmission). Mathematical models suggest that this number will vary in different locations because of variability in factors such as the baseline infection rate, vectorial capacity, efficacy of the MDA regimen used, and MDA compliance rates.^{3,4} MDA programs never achieve 100% compliance, and clinical trials have shown that *W. bancrofti* infections are only rarely cleared by a single dose of DEC with albendazole.^{22,29} Additional rounds of MDA should improve cumulative compliance rates (the percentage of people who have taken one or more doses of MDA) and improve mf clearance rates in infected people.³⁰ Although five rounds is a reasonable guideline for planning MDA programs, GPELF guidelines call for repeating MDA until targets are reached.⁶ We believe that it may be possible to eliminate LF with less than five rounds of MDA in some areas, but six rounds will not do the job if compliance rates are low.

Our results clearly show the important influence of MDA compliance on residual infection rates after MDA. It was not surprising that residual infection rates were highest in people who reported that they had never taken MDA. Although a single dose of MDA had a significant impact on mf, two doses of MDA were better than one and as good as five doses for clearing mf. In addition, although these results could be affected by inaccurate recall of MDA compliance in our study population, they are consistent with data from a clinical trial that reported dramatic increases in mf clearance rates after heavily infected subjects were treated with two or more annual doses of DEC with albendazole.^{22,30} Thus, our data emphasize that MDA programs should focus on the objective of delivering two or more doses of DEC with albendazole to a high percentage of their target populations. Note that this does not mean that LF elimination can be achieved with two rounds of MDA. It is also important to consider that these results from Egypt might not apply to all LF-endemic areas. Additional MDA doses might be needed to achieve high rates of mf clearance in areas with higher baseline LF prevalence rates and infection intensities.

Filarial infection rates should decrease over time in people who do not take antifilarial medications after LF transmission is interrupted in their area by MDA. Thus, MDA should indirectly benefit noncompliant people because of a "herd treatment effect." This effect may occur because filarial worms have a finite life span (estimated to be 7–10 years); old worms die, and new infections should be prevented by MDA. We observed a trend toward reduced infection rates in noncompliant people after several rounds of MDA, but this change was not statistically significant. This finding may have been observed because our study was underpowered to observe this decrease; only 79 of 1,064 people studied after MDA round 5 reported that they had never taken MDA.

The flip side of the herd treatment effect is that systematically noncompliant people (*al-rafidin* in Arabic) threaten the success of MDA programs, especially in areas with high baseline infection rates. Other investigators have grappled with this problem.^{8,9} It is expensive to provide supplemental rounds of MDA to entire populations in hopes of treating people who have been missed in the early rounds. Additional rounds of MDA after rounds 4 or 5 mostly treat people who do not need further treatment and miss most of the systematically noncompliant population. Further work is needed to understand the reasons for noncompliance with MDA, to refine health education message(s) to target the noncompliers, and to implement alternative strategies for crossing the finish line. These might include anti-mosquito measures, DEC-impregnated salt, or test and treat activities that permit selective treatment of people with residual infections.

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