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Review Article

The Impact of Mass Drug Administration on Lymphatic Filariasis

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Mass drug administration (MDA) has made a significant impact on the control of lymphatic filariasis (LF) since the establishment of the Global Programme to Eliminate Lymphatic Filariasis. However, its implementation is associated with several challenges, hampering interruption of parasite transmission and LF elimination in endemic areas. This study assessed the impact of MDA by comparing baseline microfilaria and antigen prevalence with those after three years (mid-term) and ≥5 years of MDA implementation and their respective prevalence reductions and identified specific challenges that may hinder its effective implementation. Three years of MDA implementation were observed to have microfilaria prevalence reductions (88.54% to 98.66%) comparable to those of studies that implemented MDA for five to 10 years (≥5 years, 79.23% to 98.26%). Inadequate community understanding of and participation in the LF MDA programme are major drawbacks to its effective implementation. The implementation of MDA that incorporates community participation, incentivisation, education, and training strategies has the potential of increasing MDA coverage and compliance, thereby interrupting parasite transmission and reducing microfilarial prevalence to levels that warrant LF elimination.

1. Introduction

Lymphatic filariasis (LF) is a debilitating, neglected tropical disease caused by three species of parasitic worms: *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori*. These arthropod-borne nematodes are transmitted to humans by the bite of infected mosquitoes in the genera *Culex*, *Anopheles*, *Mansonia*, and *Aedes*. Globally, 51.4 million people are estimated to be infected with LF [1], and the disease can compromise the health of victims and have an enormous socioeconomic burden [2, 3].

In 1997, following major advances in diagnosing and testing for LF infection and improved understanding of the epidemiology and treatment of chronic LF-related disease, the 50th World Health Assembly resolved to eliminate LF as a public health problem [4]. Subsequently, the World Health Organization (WHO) in the year 2000 established the Global Programme to Eliminate Lymphatic Filariasis (GPELF) to assist member states in achieving this goal by 2020 through morbidity management and preventive annual mass drug administration (MDA) [5].

Mass drug administration involving the two principal regimens of albendazole plus either ivermectin or diethylcarbamazine [DEC] for 4–6 years [6] or the exclusive use of table salt or cooking salt fortified with DEC for 1-2 years [7] has been implemented in various settings with varying degrees of successes and challenges. This study assessed the impact of MDA implementation on the control of LF in endemic areas and identifies specific challenges that may hinder effective implementation of MDA and reduction in microfilarial prevalence to levels below target thresholds [8] to warrant LF elimination.

2. Materials and Methods

2.1. Search Strategy. The search for relevant literature published in English language was carried out in the PubMed Central data-base from 19 December 2021 to 4 January 2022 using the search terms: "lymphatic filariasis, mass drug administration, effect, prevalence" with no limit to years. Details of the review protocol (Text S1) are registered with the OSF Registries (Registration DOI: 10.17605/OSF.IO/YQSPT) and

can be accessed (osf.io/ct6rb). This review and the selection of relevant literature were undertaken using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines [9].

2.2. Eligibility Criteria. The review employed stringent eligibility criteria. Based on the recommendation of WHO's Technical Advisory Group on the Global Elimination of LF on the assessment of the impact of MDA [10], studies from the baseline that have carried out a series of mass drug administration (MDA) using the two principal regimens [6, 7] but not reported on transmission assessment surveys (TASs) and verification of LF elimination were included in the review. Studies which reported on prevalence of LF, an indicator in the operational definition of LF elimination [11], and the primary outcome of interest in this review were included. Studies which did not meet these criteria, including those reporting on LF prevalence without MDA, missed rounds of MDA, mono- and triple-therapies against LF, control of LF using mosquito nets and MDA, LF mapping, systematic reviews, and coinfections were excluded from the review.

2.3. Method of Study Selection, Data Collection, and Analysis. The studies for the review were selected using a similar relevant article identification approach described previously [12]. The articles were screened independently by reading the titles to exclude nonlymphatic filariasis studies. The abstracts of lymphatic filariasis studies were read to assess their relevance based on the inclusion criteria. Full text articles deemed to be relevant were downloaded and used for the review.

Each relevant full text article was read to document its characteristics: country, setting, population, drugs administered in MDA programme, MDA coverage, and compliance. Data on microfilaria (Mf) and Mf antigenic cases reported at baseline, three years (mid-term), and ≥5 years (pretransmission assessment survey, pre-TAS) of MDA implementation were extracted and used to calculate their respective prevalence using the following equation:

$$P = \frac{\text{nc}}{N} \times 100\%, \quad (1)$$

where P = prevalence, nc = number of cases, and N = sample size. The percentage reductions for mid-term and pre-TAS microfilaria and Mf antigen prevalence compared to baseline prevalence were calculated using the following equations:

$$\text{MPR} = \frac{\text{BP} - \text{MP}}{\text{BP}} \times 100\%, \quad (2)$$

$$\text{PPR} = \frac{\text{BP} - \text{PP}}{\text{BP}} \times 100\%, \quad (3)$$

where MPR = mid-term prevalence reduction, BP = baseline prevalence, MP = mid-term prevalence, PPR = pre-TAS prevalence reduction, and PP = pre-TAS prevalence.

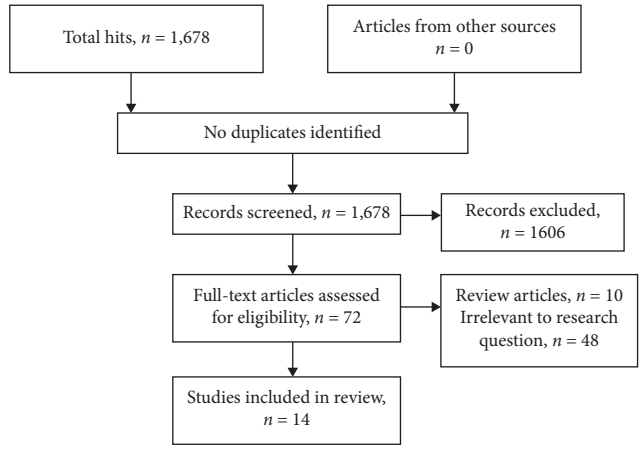

Figure 1: Flow chart of study selection process (PRISMA guide).

2.4. Definition of Variables. Prevalence in this review is the proportion of persons diagnosed as having microfilaria (Mf) of any of the LF parasites or Mf antigen in their blood and was calculated before (baseline), three years (mid-term), and ≥5 years (pre-TAS) of MDA implementation. MDA coverage is the percentage of the population at risk of LF covered by MDA, and compliance with MDA is the percentage of persons who ingested the prescribed drugs during MDA implementation in an LF endemic area.

2.5. Risk of Study Bias Assessment. The risk of bias in individual studies was assessed independently by reviewers using the quality assessment tool developed for prevalence studies [13]. It was based on the assignment of numbers to a yes (0, low risk) and no (1, high risk) answers for ten parameters (Supplemental Table S1) on the external and internal validity of the studies. The overall study quality assessment was determined by summing up the assigned numbers based on the levels of risk of bias categorized as low (≤2), moderate (3-4) or high (≥5).

3. Results

3.1. Study Selection and Risk of Bias Assessment. A total of 1,678 results were obtained from the PubMed Central literature search out of which 14 were deemed to be relevant to the research question. Figure 1 shows the study selection process.

Based on the risk of bias assessment of the 14 studies included, 9 (64.3%) and five (35.7%) were observed to have low and moderate risks of publication bias, respectively (Supplemental Table S1).

3.2. Data Extraction. Characteristics of the relevant lymphatic filariasis studies extracted are presented in Table 1. Based on the assessment of the impact of mass drug administration (MDA) on lymphatic filariasis (LF) control, data on microfilaria (Mf) and Mf antigenic cases reported at baseline, three years (mid-term), and ≥5 years (pretransmission assessment survey, pre-TAS) of MDA

Table 1: Mass drug administration coverage and compliance in lymphatic filariasis studies included in this review.

Reference, country	Setting and population (age group, years)	Drug administered in MDA programme	MDA coverage or compliance (%)
[14], Mali	Inhabitants of villages (≥2)	Albendazole and ivermectin	>67
[15], American Samoa	Household members in villages (≥2)	Diethylcarbamazine and albendazole	(*56, 19–71)
[16], Egypt	Community members (>5)	Diethylcarbamazine and albendazole	>85
[17], Sierra Leone	Community members (>5)	Albendazole and ivermectin	82.5–88.5
[18], Sierra Leone	Community members (>5)	Albendazole and ivermectin	75.9–79.6
[19], Nigeria	Community members (>5)	Albendazole and ivermectin	72.2–96
[20], Egypt	Village surveys (≥2)	Diethylcarbamazine and albendazole	>†80
[21], India	Community members, —	Diethylcarbamazine-medicated salt	100
[22], Tanzania	Students (≥1)	Albendazole and ivermectin	62.1–94.8
[23], Tanzania	Standard 1 pupils (7.5–8.1)	Albendazole and ivermectin	87.7–94.5
[24], Tanzania	Students and community members (≥1 and ≥10)	Albendazole and ivermectin	75–98.7
[25], Tanzania	Students and community members (≥10)	Albendazole and ivermectin	46–56
[26], Indonesia	Residents in villages (≥5)	Diethylcarbamazine and albendazole	†70.1–89.8
[27], Papua New Guinea	Residents of rural villages (≥2)	Diethylcarbamazine and albendazole	†72.9

†Compliance; MDA, mass drug administration; —: data not available; *mean MDA coverage.

implementation were extracted and presented in Table 2. Baseline, mid-term and pre-TAS microfilaria (Table 3) and Mf antigen (Table 4) prevalence were calculated. The percentage reductions for mid-term and pre-TAS microfilaria (Table 3) and Mf antigen (Table 4) prevalence compared to baseline prevalence were also calculated.

4. Discussion

4.1. Impact of MDA on Lymphatic Filariasis Control. One of the two strategies to achieve the goal of lymphatic filariasis (LF) elimination is preventive chemotherapy [28] delivered through mass drug administration (MDA), aimed at interrupting LF transmission. MDA involving albendazole plus either ivermectin or diethylcarbamazine [DEC] for 4–6 years [6] or the exclusive use of table salt or cooking salt fortified with DEC for 1-2 years [7] is recommended for effective control of LF [29]. Albendazole and ivermectin are administered in areas where LF is co-endemic with onchocerciasis, as observed in sub-Saharan Africa [30]. However, treatment with DEC is contraindicated in areas where onchocerciasis or loiasis might coexist [29], accounting for its use in onchocerciasis-free regions. This is due to the potential for severe adverse events such as the induction of strong local inflammation in patients with ocular microfilariae attributable to microfilariae death [31]. These regimens, at adequate levels of coverage, safely and effectively reduce the number of microfilariae circulating in the blood and, therefore, the prevalence of infection in the entire LF endemic community [11].

This review assessed the impact of MDA implementation by comparing baseline microfilaria and antigen prevalence with those of three years (mid-term) and ≥5 years (pre-TAS) and their respective percentage reductions. Although the stringent eligibility criteria limited the number of articles, this review provides useful information for stakeholders in the control of LF. In this review, 11 (78.57%) and three (21.43%) studies reported variable MDA coverage (19% to 100%) and compliance (70.10% to 80%), respectively (Table 1), highlighting the challenge of attaining and maintaining high treatment coverage. To achieve interruption of parasite transmission, MDA coverage of at least 80% [32] and compliance exceeding 65–75% [33] are required.

The percentage microfilaria (Mf) prevalence reduction three years after MDA implementation was high, ranging from 88.54% to 98.66% in the majority of the mid-term studies (4 [80%], Table 3), with one reporting a low prevalence reduction of 58.74%. Interestingly, these reductions are comparable to those of studies that implemented MDA for five to 10 years (≥5 years) with a majority of them (5, 83.33%) having prevalence reductions ranging from 79.23% to 98.26% (Table 3) with one unusually increasing in Mf prevalence by 36.15% attributable to very low MDA coverage of 46–56% [25]. The percentage antigen prevalence reductions at three years and five to 10 years of MDA implementation compared to baseline antigen prevalence appeared to be comparable (Table 4). Various studies have reported that two [16, 34] or three [18] years of MDA implementation with high coverage (≥80%) have a similar impact on the reduction of LF prevalence compared with ≥5 years of MDA recommended for interruption of parasite transmission [32]. They suggest that effectively addressing the challenges of MDA implementation has the potential to cause an early interruption of parasite transmission, thereby reducing the years of MDA implementation. These findings highlight the importance of effective implementation of MDA in LF control.

Table 2: Microfilaria and antigenic cases at baseline and after MDA implementation reported by lymphatic filariasis (LF) studies.

Reference, country	Diagnostic method	Baseline LF cases (*N*)		LF cases (*N*); years of MDAI	
		Mf	*Antigen	Mf	*Antigen
[14], Mali	Thick blood film & ICT	—	244 (1139)	—	0 (760); 6
[15], American Samoa	Thick blood smear & ICT	—	483 (3018)	5 (1881); 6	43 (1881); 6
[16], Egypt	Thick blood smear, ICT & RACT	115 (1000)	190 (1000)	2 (1000); 5	27 (1000); 5
[17], Sierra Leone	Thick blood film	214 (8233)	—	18 (6023); 3	—
[18], Sierra Leone	Thick blood film	214 (8233)	—	23 (4230); 5	—
[20], Egypt	Thick blood film & ICT	274 (1877)	612 (1877)	22 (1828); 5	144 (1828); 5
[21], India	Thick blood film	678 (14963)	—	4 (6649); 3	—
[19], Nigeria	Thick blood smear & ICT	206 (4198)	527 (2439)	15 (1720); 7–10	127 (1720); 7–10
[22], Tanzania	Counting chamber	225 (919)	—	68 (674); 3	—
[23], Tanzania	Finger-prick blood & ICT counting chamber & ICT	—	210 (888)	—	101 (953); 3 49 (855); 4
[24], Tanzania	Counting chamber & ICT	225 (919)	—	11 (393); 6	77 (393); 6
[25], Tanzania	Counting chamber & ICT	225 (919)	—	20 (60); 8	69 (422); 8
[26], Indonesia	Thick blood smear & ICT	193 (2165)	47 (722)	5 (1776); 3	10 (871); 3
[27], Papua New Guinea	Membrane filtration & RACT	106 (757)	265 (558)	7 (529); 3	93 (543); 3

*Cases based on Mf antigen using the immunochromatographic test (ICT) or rapid-format antigen card test (RACT); Mf, microfilaria; *N*, sample size; MDAI, mass drug administration implementation; —: data not available.

Table 3: Percentage microfilaria prevalence reduction at mid-term and pretransmission assessment survey (pre-TAS) compared to baseline prevalence in LF mass drug administration.

Reference, country	Baseline Mf prevalence (*N*)	LF prevalence (*N*); *% PR	
		Mid-term Mf	Pre-TAS Mf
[16], Egypt	11.50 (1000)	—	0.20 (1000); 98.26
[17], Sierra Leone	2.60 (8233)	0.30 (6023); 88.54	—
[18], Sierra Leone	2.60 (8233)	—	0.54 (4230); 79.23
[20], Egypt	14.60 (1877)	—	1.20 (1828); 91.78
[21], India	4.53 (14963)	0.06 (6649); 98.66	—
[19], Nigeria	4.91 (4198)	—	0.87 (1720); 82.28
[22], Tanzania	24.48 (919)	10.10 (674); 58.74	—
[24], Tanzania	24.48 (919)	—	2.80 (393); 88.56
[25], Tanzania	24.48 (919)	—	33.33 (60); †36.15
[26], Indonesia	8.91 (2165)	0.28 (1776); 96.86	—
[27], Papua New Guinea	14 (757)	1.32 (529); 90.57	—

Mf: microfilaria; LF: lymphatic filariasis; *N*, sample size; pre-TAS: pretransmission assessment survey; *% PR, percentage prevalence reduction compared to baseline prevalence; —: no data available; †increase in prevalence.

Table 4: Percentage antigenic prevalence reduction at mid-term and pre-TAS compared to baseline prevalence in LF mass drug administration.

Reference, country	Baseline antigen prevalence (*N*)	LF antigen prevalence (*N*); *% antigen PR	
		Mid-term	Pre-TAS
[14], Mali	21.42 (1139)	—	0 (760); 100.00
[15], American Samoa	16.00 (3018)	—	2.29 (1881); 85.69
[16], Egypt	19.00 (1000)	—	2.70 (1000); 85.79
[20], Egypt	32.61 (1877)	—	7.88 (1828); 75.84
[19], Nigeria	21.61 (2439)	—	7.38 (1720); 65.85
[23], Tanzania	23.65 (888)	10.60 (953); 51.18	—
[26], Indonesia	6.51 (722)	1.15 (871); 82.33	—
[27], Papua New Guinea	47.49 (558)	17.13 (543); 63.93	—

LF: lymphatic filariasis; *N*: sample size; pre-TAS, pretransmission assessment survey; *% antigen PR, percentage antigen prevalence reduction compared to baseline antigen prevalence; —: no data available.

4.2. Challenges of MDA Implementation. The implementation of MDA in LF control is associated with several challenges such as low compliance [35] and the difficulty attaining and maintaining of high treatment coverage [36, 37]. Widespread noncompliance may increase the number of individuals serving as reservoirs of infection in the population, thereby increasing the chance of LF transmission [16, 32]. Inadequate community understanding of and participation in LF MDA programme is, therefore, a major drawback to its effective implementation. Moreover, the difficulty in retaining community health volunteers, involved in training and drug distribution, on account of low financial incentives [38], inaccurate [39, 40], and late data reporting on LF treatment coverage [41] has also been documented. These challenges create the opportunity for LF parasites to remain in circulation in endemic areas, making interruption of their transmission difficult.

4.3. Implications for Lymphatic Filariasis Elimination. Mass drug administration (MDA) for LF control is aimed at reducing the density of parasites circulating in the blood of LF victims and the prevalence of infection in communities to levels where transmission is no longer sustainable by the mosquito vector [6]. In this regard, community participation in MDA programmes is highly recommended. The involvement of opinion, traditional, and religious leaders in MDA implementation campaigns will generate interest in and acceptance of the programme and, thus, enhance cooperation and programme participation.

Educating community members on the importance of the programme, the safety of the drug, and its side effects will allay their fears and should be an integral part of MDA programmes. Provision of incentives in the form of bed nets to community members [42] and adequate allowances to community health volunteers for training and drug distribution [43, 44] has the desired effects of increasing drug uptake and community participation. The use of convenient period for drug distribution may also increase drug uptake, as absence from home during drug distribution is an important reason for not taking the drugs [36]. These strategies are likely to increase compliance with MDA and MDA coverage to the required levels [32, 33] to interrupt parasite transmission and reduce microfilarial prevalence to levels that warrant LF elimination.

5. Conclusion

This study revealed high microfilaria (Mf) prevalence reductions for studies that implemented MDA for LF control

for three years, comparable to those of studies that implemented MDA for five to 10 years. However, variable MDA coverage ranging from 19% to 100% was reported, highlighting the challenge of attaining and maintaining the high LF treatment coverage (≥80%) required to achieve interruption of parasite transmission. Mass drug administration (MDA) for LF control should aim at drawing attention to the importance of the programme and improving its understanding as well as community participation. This approach is fundamental to increasing compliance with MDA and MDA coverage, thereby interrupting parasite transmission.

Data Availability

No primary data were used to support this study. Information presented in this review is based on published papers which have been duly cited.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Supplementary Materials

Details of the review protocol (Text S1) is registered with the OSF Registries (Registration DOI: 10.17605/OSF.IO/YQSPT) and can be accessed (osf.io/ct6rb). The risk of bias assessment of the studies included in this review is reported in Supplemental Table S1. (*Supplementary Materials*)

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