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Melanie Strahm Date

Assessing the impact of Mass Drug Administration (MDA) in the Global Programme to Eliminate Lymphatic Filariasis (GPELF) on Patients with Filarial Disease

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Abstract

Assessing the impact of Mass Drug Administration (MDA) in the Global Programme to Eliminate Lymphatic Filariasis (GPELF) on Patients with Filarial Disease

By Melanie Strahm

Background: Lymphatic filariasis (LF) is a chronically disabling and debilitating mosquito-borne parasitic infection that infects an estimated 120 million persons worldwide. LF is endemic in 81 countries with approximately more than 1.3 billion people at risk of infection worldwide. The Global Programme for the Elimination of Lymphatic Filariasis (GPELF) was launched in 2000, and as of 2009 scaled up to introduce MDA in 53 endemic countries. The GPELF focuses on the interruption of transmission through mass drug administration and managing and preventing disability, such as ADL, lymphedema, and hydrocele, for infected individuals.

Objective: The objective of this analysis was to evaluate studies assessing the impact of mass drug administration on filarial morbidity.

Methods: Studies were included from a Pubmed search via criteria established a priori. Analysis was performed on studies that met the standards based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for rating evidence.

Results: Data from 25 studies met the criteria for inclusion. Of these, ten evaluated ADL events, 15 assessed lymphedema, and 15 assessed hydrocele outcomes. Study design included 14 clinical trials and eleven prospective cohort, case study, or cross sectional evaluations. Of the included studies, 15 studies were considered to be of sufficient quality for in depth analysis. Five studies reported a decrease in ADL events over the course of the study period. Improvement was noted in five studies, and a lack of improvement was found in four studies assessing lymphedema and/or elephantiasis. Hydrocele was found to improve in five studies, whereas no improvement was recorded in four.

Conclusion: The data suggests inconclusive results derived from studies assessing the impact of MDA on LF morbidity. Studies on MDA and clinical disease demonstrate numerous inconsistencies related to methodology. The mixed results of this review stress the need to adopt and employ more rigorous and standardized case definitions, study design, and outcome measurements to better understand and respond to the course of clinical disease after MDA employment.

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I. INTRODUCTION

Since the inception of the Global Programme to Eliminate Lymphatic Filariasis (GPELF) in 2000, most of the attention on disease elimination has focused on the interruption of disease transmission with efforts targeting morbidity taking second stage [1-3]. However, with mass drug administration (MDA) programs successfully reducing microfilaremia rates in targeted communities, more attention has been placed on the need to follow the long term disabling effects of filarial disease, namely adenolymphangitis (ADL), hydrocele and lymphedema. This awareness has led to an increased number of studies incorporating morbidity assessment as an outcome for monitoring the success of MDA [4]. Additionally, GPELF has increased its efforts regarding response to morbidity related issues. Activities based on morbidity prevention have involved educational events at local hospitals, community wide trainings, and patient care tutorials within the context of complex and diverse settings. Most of these actions have occurred as the result of previous research focusing on the benefits of interventions like basic hygiene on preventing physical disease progression. Despite this increase in awareness, morbidity improvement, in particular, has not been considered in depth as a consequence of MDA, and existing literature indicates there is little consistency on how to regard previous research and the best way to approach future assessments in a standardized manner.

From 2000 to 2009, 695 million individuals received MDA treatment. Yet, despite such widespread treatment, 40 million people remain plagued with the long-term consequences of LF morbidity. Studies following MDA have generally concentrated on the effects of chemotherapy on microfilaremia levels. Less effort has been devoted to

morbidity prevention than hematological elimination, and victims of LF morbidity are often neglected in research concentrating on MDA outcomes. In 2007, a study by Addiss, et al., pointed to the need to prioritize research on the influence of mass antifilarial drug treatment administration on the course of filariasis-associated disease in order to better direct and/or enhance morbidity management strategies. Of the studies on MDA published over last decade, only a few have concentrated exclusively on the specific manifestations of ADL, lymphedema, and hydrocele [4].

LF related morbidity leads to devastating effects on the health and wellbeing of those afflicted and exacts a heavy toll on the community at large in terms of lost economic productivity. Unfortunately, all residents of endemic areas are susceptible to infection via repeated exposure from mosquito introduced microfilariae since childhood. With an underlying infection of worms infiltrating the lymphatic system of its victims, the tissue damage exacted by the total worm burden and eventual adult worm death lead to the display of LF signs and symptoms. Restriction of the normal lymph flow causes swelling, scarring, fibrosis and increased susceptibility to infection. The legs and groin are most affected by the progression of lymphatic damage. As a result, victims are often left disabled and without the resources to understand or deal with the advanced stages of disease. Without providing these individuals with the proper modalities of care, acute inflammatory attacks continue with impunity and thus contribute to lymphedema aggravation and the eventual formation of elephantiasis in 5% of those infected. Similarly, testicular hydrocele characterizes a disfiguring enlargement of the scrotum which can grow to devastating proportions, reducing mobility, limiting work capacity, and inhibiting sexual performance [5]. Much of the pathogenesis related to LF morbidity

is poorly understood, and as a result, misunderstandings of etiology have prevented the rapid evolution of a standardized method to management. However, recent research has accelerated the understanding of how to address morbidity. While more is known regarding biology, there still remains a deficit in knowledge regarding the relationship between MDA and those already afflicted with morbidity.

Previous evaluations dating back to the 1950s regarding MDA have mostly concentrated on the drug diethylcarbamazine, DEC, and its influence on microfilaranemia as a primary endpoint. This makes sense given the then current tools available to monitor MF blood levels and the fact that DEC has been viewed as the only viable tool in the arsenal of MDA options up until the introduction of ivermectin and albendazole. Thus, the point of earlier investigations has been to evaluate DEC's effectiveness in the fight to interrupt LF transmission in endemic areas at the population level. In addition to evaluating MF levels, studies have also delved into comparing dosing regimens, assessing side effects and tolerability, and, as an aside, effects on clinical morbidity. Since clinical morbidity has rarely served as the topic of main interest, a majority of these studies neglected to formalize a clear and uniform case definition. There is wide heterogeneity in definitions regarding the morbidity of interest, and, interestingly, a lack of consistency on what aspect of clinical morbidity to prioritize. For example, some studies have followed acute disease alone, while others have focused primarily on chronic manifestations, and very few on both. A reason for this results from the follow up periods available to the investigator. With limited funding and time, it is not surprising that the monitoring of chronic disease would take the back burner to more tangible and immediate endpoints. Attempts to follow chronic disease in the form of

lymphedema and hydrocele over the short term might not be expected to capture a noticeable difference. Also, the logistics of finding those suffering from transient ADL or relying on a history of symptoms to define ADL does not lend itself to reliable reporting.

The systematic literature review conducted for this thesis explores research regarding GPELF's mission to reduce the burden of morbidity via mass drug administration and what is currently understood regarding the underlying mechanism behind LF induced ADL, lymphedema, and hydrocele morbidities. While the biology of MDA's impact on morbidity has not been extensively researched, there are available studies with data exploring the effects of MDA on predetermined measures of morbidity (reduction in size, reduction in ADL frequency, or reduction of the incidence of new cases).

Given the fact that GPELF would benefit from sound data in order to be prepared to deal with existing morbidity and given the fact that no study has exclusively concentrated on MDA and filarial morbidity to date, a review of studies relating MDA and morbidity is necessary to assess if MDA, in fact, positively affects morbidity and which medications work the best on a large scale to reduce overall burden. In concert with the goals of the GPELF to address MDA and morbidity as primary targets of interest, research will focus on the comparison and evaluation of studies following the clinical manifestations of lymphatic filariasis after MDA, specifically selecting studies performing a clinical assessment of ADL, lymphedema, and/or hydrocele. Ultimately, this research will provide better insight on how MDA drugs impact LF morbidity.

II. LITERATURE REVIEW

Lymphatic filariasis (LF)

Lymphatic filariasis (LF) is a mosquito-borne parasitic infection caused by three different parasites: Wuchereria bancrofti, Brugia malayi, and Brugia timori [6, 7]. Approximately, 90% of infections are caused by Wuchereria bancrofti, and most of the remaining infections are caused by Brugia malayi. LF represents one of the oldest and most clinically significant neglected tropical diseases. An estimated 120 million people in 81 countries are presently infected, and an estimated 1.34 billion live in areas at risk of infection where filariasis is endemic, defined as areas where the prevalence of microfilaraemia or antigenaemia is $\geq 1\%$ [3]. Sadly, approximately 40 million people suffer from the economically, socially, and physically disabling clinical manifestations of the disease, including 15 million displaying grossly enlarged extremities in the form of lymphedema (elephantiasis) and 25 million men exhibiting urogenital swelling, most noticeably scrotal hydrocele.

Humans are the primary reservoirs for lymphatic filariasis [8, 9]. Transmission of the parasite from person to person occurs through a mosquito vector. Several mosquito species are able to transmit W. bancrofti with the most common species being Culex quinquefasciatus in the Americas, Anopheles in Africa, and Aedes and Mansonia in Asia and the Pacific. In order to transmit of the parasite, the mosquito becomes infected with microfilariae (MF) during a blood meal. Within the mosquito, MF typically spend 7-21 days developing into infective third-stage larvae. Microfilariae are transmitted to the human host via the subsequent blood meal where they make their way to the lymph vessels and mature into adult worms; there females shed microfilariae which circulate at

night in the peripheral blood. Adults may continue to live within the host for four to six years. Infection is normally acquired in childhood or adolescence after repeated exposure to MF [10].

Due to advances in technology, diverse methods of identifying LF infection in humans now exist. LF diagnosis is often made on clinical grounds, supported by eosinophilia and sometimes by positive serology [11]. The following, diagnostic techniques highlighted from a case report on lymphatic filarisis, offers various options for detecting infection:

1) Night blood survey: Definite diagnosis of lymphatic filiarasis depends on demonstration of living parasite in the human body, this is done by:

- Thick film: Microfilariae in the blood are visualized at night.
- Membrane filter concentration method: Microfiltration of a sample of lysed blood; sensitive for detecting microfilaraemia at low densities.
- DEC provocation test: 50-100 mg of DEC is given to a patient and a blood sample is taken 30-45 minutes later looking for the presence of microfilariae. DEC may produce an initial exaggeration of symptoms following administration.

2) Serological tests: Indirect fluorescence and enzyme-linked imunosorbent assay to detect antibodies for LF.

3) Xenodiagnosis: Mosquitoes are allowed to feed on the patient and then dissected 2 weeks later.

4) Ultrasonography: A 7.5 MHz or 10 MHz probe can locate and visualize the movements of living adult worms in the lymphatics of asymptomatic patients

with microfilaraemia. The constant thrashing movements described as “Filaria dance sign” can be visualized [7, 12].

5) Lymphoscintigraphy: The structure and function of the involved limb's lymphatic involvement can be assessed after injecting radiolabeled albumin or dextran in the web space of the toes. Next, imagery with a Gamma camera can reveal structural changes such as lymphatic dilation in the early asymptomatic stage of the disease [13, 14].

6) X-ray: Calcified filariae may be demonstrated by radiography.

A highly sensitive and specific card test can detect circulating filarial antigen (CFA) in the blood at any time of day [15]. Less resource-intensive, the test requires only a finger prick blood sample making it more applicable in resource-poor settings. Research has suggested that increased CFA correlates with increased density of MF in the bloodstream. Unfortunately there is no gold standard for ruling out the presence of adult worms in infected individuals [16].

Global Programme to Eliminate Lymphatic Filariasis (GPELF)

In 1993, the International Task Force for Disease Eradication listed LF as one of only six “eradicable or potentially eradicable” diseases [17]. As of 1997, the World Health Assembly requested Member States to develop national plans for interventions with the final endpoint of LF elimination. In 2000, the World Health Organization (WHO) established the Global Programme to Eliminate Lymphatic Filariasis (GPELF); GPELF serves as part of an extensive program of combined efforts to control neglected

tropical diseases [3]. These efforts include preventive chemotherapy, vector control, and morbidity management interventions offered as an integrated package with the aim of involvement at all levels of government. Currently, the ultimate goal of GPELF is to eliminate lymphatic filariasis as a public health scourge by the year 2020. Focusing efforts to achieve this goal involves two strategies: first, the interruption of LF transmission by providing combinations of two medicines en masse to the endemic population at risk (mass drug administration or MDA) and, second, the alleviation of morbidity by introducing simple interventions, such as improved hygiene and skin care, to people with lymphedema, and by providing simple surgery for men with hydrocele. Currently, GPELF has implemented MDA in 53 of the 81 LF endemic countries , and the program has successfully completed five or more annual rounds of MDA in 37 countries; however, only 27 countries currently practice active morbidity-management with established programs.

Mass Drug Administration

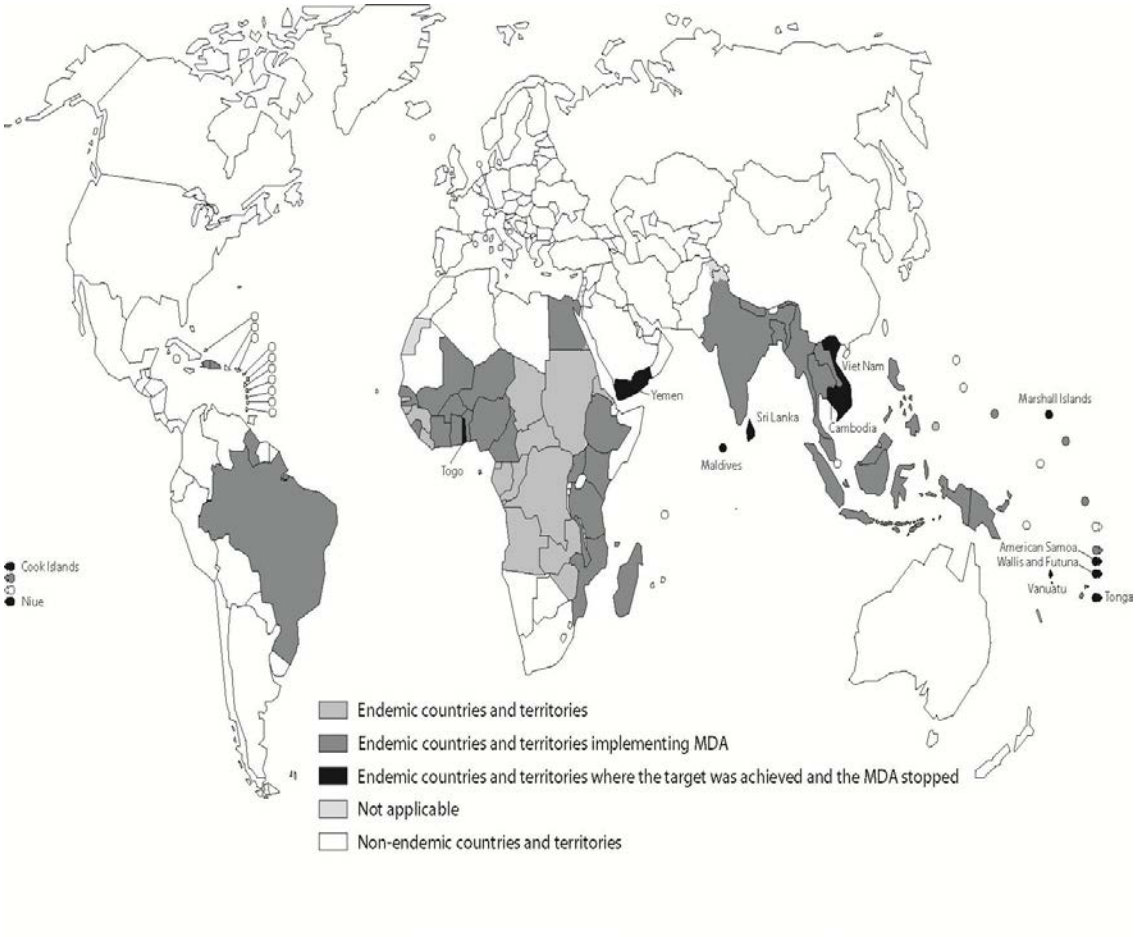
Mass Drug Administration (MDA) represents the most integral component in achieving successful GPELF elimination of LF by 2020 [3]. The underlying reason for this partially resides in the ability to monitor the direct effects of mass chemotherapy with a simple blood test, and the GPELF's capacity to scale up programming over the past decade. So far, the success of elimination is determined by demonstrating a reduction in the numbers of circulating microfilariae in infected individuals within a geographic area [18]. As an indication of success, more than 2.8 billion treatments have been administered since GPELF's inception to 845 million people [3].

According to the WHO, the recommended regimens for MDA currently are:

- once-yearly treatment with a single dose of two medicines given together– albendazole (400 mg) plus either ivermectin (150–200 mcg/kg) or DEC (6mg/kg) for 4–6 years; or
- exclusive use of table and cooking salt fortified with DEC for 1–2 years.

In 2009, combination therapy of diethylcarbamazine (DEC) plus albendazole, or ivermectin plus albendazole was distributed to eligible individuals in every endemic country, excluding Brazil. Of those receiving MDA, 82.49% of those eligible for preventive treatment received DEC and albendazole in countries where onchocerciasis is not co-endemic with LF, 17.48% received ivermectin and albendazole in countries where onchocerciasis is co-endemic with LF, and 0.03% received DEC alone [19, 20].

Figure 1 Countries where lymphatic filarisis is endemic and status of mass drug administration (MDA) in those countries, 2010



Morbidity

LF infected individuals may eventually demonstrate severe clinical manifestations with disabling disfigurement of the limbs and genitals, specifically ADL, and the chronic manifestations of lymphedema and hydrocele. Approximately 40 million people suffer from the stigmatizing and aggravating clinical manifestations of the disease [3]. In areas endemic to the filarial parasite, children are the first victims of infection. However, clinical signs and symptoms of the disease characteristically remain quiescent until after puberty. Although MDA has produced largely successful results and executed effective efforts at scaling up at an incredible pace, the same response has not occurred through

labors targeting LF morbidity. Disability treatment and prevention for patients with filarial morbidity includes basic management of lymphedema for those with the condition and simple surgery for men with hydrocele [21]. Lymphedema management involves cleansing the affected leg, early treatment of bacterial and fungal infections, elevation, and exercises [22]. Clinical and histopathological studies suggest that improving hygiene and care of the skin can both decrease the number of acute and painful inflammatory episodes [23-26] and stop the progress of or, in some cases, partially reverse disease progression [4, 24, 26-30]. Currently global efforts are aware of the need to expand morbidity related services for all affected sufferers. To address this, morbidity research over the past 10 years has primarily concentrated on techniques to detect clinical disease in children treated with MDA [14, 31-33]; outcomes related to hygiene and skin care [4, 34]; influences of MDA on morbidity [35, 36]; responses to MDA compliance based on morbidity management [34]; considerations of the economic and psychosocial burdens of chronic morbidity [37], and techniques for diagnosis and surgical repair of hydrocele [12, 34].

Adenolymphangitis (ADL)

ADL present as localized inflammation of the skin with involvement of the nodes and lymphatic vessels accompanied by fever [38]. Typically, ADL lasts from a few days to one to three weeks at a time and may occur multiple times per year as episodes of extreme pain [39]. Contributing to an ongoing problem concerning the development of sound data to understand the effects of drug administration on the effects of LF is a lack of consensus among researchers on how to define ADL or “acute attack.” Unlike evidence of chronic infection, ADL proves less specific and more varied in terms of

duration, physical presentation, and symptoms. There is longstanding debate on the extent and pathogenesis of ADL. From clinical data in the 1940s, LF morbidity was originally grouped into primary, secondary or tertiary filariasis: a primary case developed acute filarial fever or lymphangitis; secondary cases occurred at adenopathy onset; and tertiary cases yielded hydrocele and elephantiasis [40]. However, this original division proved problematic given that clinical manifestations often overlap one another and symptoms of acute disease, chills, fever and malaise, easily mimic a plethora of disease states endemic to the geographical regions with ongoing control programs.

Studies into the 1950's divided clinical LF into either acute or chronic cases. Hewitt's study in British Guiana on MDA and clinical disease first reported acute cases as demonstrating lymphangitis, lymphadenitis, filarial fever, orchitis, abscess, or severe abdominal pain at follow up after administration of DEC [41]. Most of the early studies evaluating MDA and ADL have included lymphangitis and acute filarial fever as representative of ADL while defining the onset of enlarged glands as chronic in nature [36, 40, 42, 43]. Starting with Ciferri in 1969, further research involving ADL began using adenolymphangitis [43, 44] as an identifying marker. At no point do any of the previous studies distinguish attacks based on underlying biology or describe the distinguishing features between lymphangitis and adenolymphangitis.

Many etiologies have been postulated as an underlying reason for ADL; causes have included secondary bacterial infections, immune system response to filarial antigens, and reactions mediated by the living and/or deceased adult worm [4]. These events are thought to contribute to edema progression and the exacerbation of physical impairment [45-47]. Originally acute filarial lymphangitis (AFL) was thought to

originate from the body's immune defense against dying adult worms or the result of an allergy against the filarial larvae parasite; a review by Addiss et al. described the lympangitis progressing distally along the lymphatic vessel producing a palpable cord with accompanying symptoms of fever, headache and malaise [4]. Now, further research has revealed the role of infection, particularly Group A *streptococcus*, as a major contributing factor to the origin of acute events and the eventual development of lymphedema [26, 28, 29, 48]. Symptoms due to dermal conditions, similar to cellulitis of the extremities, are grouped under the term acute dermatolymphangioadenitis (ADLA). With this expanded knowledge of the need to prevent secondary infection in order to avert ADL, morbidity management programs have become increasingly aware of the need to emphasize cleansing infected areas and attempting to minimize damage progression with treatment options including topical and oral antibiotics [10].

Even today, however, resolution has not been reached over the comprehensiveness of acute disease description. Currently there is still question over incorporating a case definition for an associated 3rd stage larva induced lymphangitis which does not fit into either the AFL or ADLA category [49]. Ideally, future research into clinical morbidity will utilize a standardized definition based on the latest known data explaining the etiologies for each unique presentation underlying acute disease, however this may involve intense clinical monitoring, bacterial culture, treatment, and diagnostic studies to determine worm death [39]. Regardless, correct clinical determination of ADL depends on establishing a consistent methodology of data collection.

Lymphedema

Lymphedema occurs through lymphatic dysfunction and dilatation due to adult filarial worms. With this disruption and loss of flow, fluid accumulates and is retained to produce tissue swelling [50]. Typically, swelling occurs in the legs, arms, breasts, scrotum, and penis. Almost 15 million people, the majority of whom are women, have lymphedema, primarily affecting a lower limb [3]. Without proper lymphatic circulation, tissues with lymphedema are vulnerable to infection. Small cuts or openings in the skin and between the toes, known as entry lesions, allow bacteria to enter and multiply which contributes to the development of ADL [29]. This cycle of lymphatic vessel damage due to repeated episodes of inflammation worsens lymphatic dysfunction and thus leads to increased risk for future episodes of ADL and, thus, further damage in the form of skin hardening and increased fluid accumulation. The advanced stage of lymphedema is known as elephantiasis which exists as one of the most common causes of disability in the world [9].

Of the published studies assessing the effect of MDA on filarial morbidity, eight out of 13 studies found a beneficial effect of MDA on lymphedema [4]. Although, there are several studies that demonstrate improvement in lymphedema in patients who adhere to a lymphedema management regimen [36, 41, 43], studies exploring the effect of MDA on filarial morbidity reach different conclusions Many patients with lymphedema do not demonstrate evidence of microfileraemia or antigenaemia which emphasizes the need to evaluate morbidity regardless of hematology studies [51]. After nine rounds of MDA, Mukhopadhyay et al. noted that out of 497 participants examined, the microfileraemia

rate was zero, but lymphedema was found among seven elderly residents [52]. Even in the wake of a successful suppression of new fiariasis infections following MDA, clinical and debilitating symptoms of chronic disease remain. Knowing how MDA drug type directly influences lymphedema will help guide the course of future program practices and evaluations. However, the magnitude of benefit is difficult to evaluate given a lack of comparable and variable data.

Hydrocele

By far the most common manifestation of LF infection, hydrocele is a condition which results from the accumulation of fluid in the tunica vaginalis of the scrotum. Filarial hydroceles differ considerably in size, sometimes growing so large that they become socially stigmatizing while also causing intense discomfort [53, 54]. Approximately 25 million men are thought to suffer from filarial hydrocele globally with 10-50% of men afflicted in LF endemic areas [55]. Although lymphedema has often been given more attention in the literature, the burden of hydrocele is far greater than morbidity due to lymphedema [56]. Hydrocele continues to contribute to a significant cause of serious financial, social, and psychological stress due to physical disfigurement, social stigma, loss of self-esteem, decreased employment opportunity, interference in sexual activity, and family conflict [54]. Economic stability is threatened by the direct costs of medical treatment, the inability to work due to episodic attacks of ADL, diminished productivity, decreased contribution to the workforce, and reduced contribution into economic and household activities [57].

MDA and Filarial Morbidity Research

There currently is not a systematic approach to the evaluation of LF morbidity after MDA administration. New guidelines for delivering MDA and protocols for halting MDA and performing subsequent surveillance, via a transmission assessment survey, have been created with the goal of dissemination in 2012. However, GPELF is still developing guidelines and training materials concentrating on morbidity management and disability prevention [2].

Given the goals of the GPELF to address MDA and morbidity as primary targets of interest, exploring the effects of mass treatment on filarial morbidity through a systemtic literature review is needed. In an effort to fill this gap in knowledge, it is necessary to concentrate on the comparison and evaluation of studies following the clinical manifestations of lymphatic filariasis after MDA, specifically selecting studies performing a clinical assessment of acute inflammatory episodes, lymphedema, and/or hydrocele. Ultimately, this research will provide insight on how MDA drugs impact LF morbidity and guide recommendations to follow based on practical evaluation methods derived from the culmination of previous experience.

III. METHODOLOGY

Search strategy

A systematic search was performed to identify relevant studies in PubMed since the 1940s until October, 2011. PubMed was utilized as the main search engine for this review due to the comprehensiveness of biomedical literature derived from diverse sources including MEDLINE, life science journals, and online books. The following presents an overview of the complete search strategy.

Result: 50 publications

Database: PubMed

User query: ((filariasis) OR lymphatic filariasis) AND (diethylcarbamazine OR DEC OR ivermectin OR albendazole) AND (hydrocele, lymphedema, OR adenolymphangitis)

Translations:

Filariasis	"filariasis"[MeSH Terms] OR "filariasis"[All Fields]
lymphatic filariasis	"elephantiasis, filarial"[MeSH Terms] OR ("elephantiasis"[All Fields] AND "filarial"[All Fields]) OR "filarial elephantiasis"[All Fields] OR ("lymphatic"[All Fields] AND "filariasis"[All Fields]) OR "lymphatic filariasis"[All Fields]
diethylcarbamazine	"diethylcarbamazine"[MeSH Terms] OR "diethylcarbamazine"[All Fields]
Ivermectin	"ivermectin"[MeSH Terms] OR "ivermectin"[All Fields]
Albendazole	"albendazole"[MeSH Terms] OR "albendazole"[All Fields]
hydrocele	"hydrocoele"[All Fields] OR "testicular hydrocele"[MeSH Terms]

Lymphedema	OR ("testicular"[All Fields] AND "hydrocele"[All Fields]) OR "testicular hydrocele"[All Fields] OR "hydrocele"[All Fields] OR "Hydrocele"[All Fields] "lymphoedema"[All Fields] OR "lymphedema"[MeSH Terms] OR "lymphedema"[All Fields]

Study selection

A set of inclusion criteria were applied to select potential studies. Of the studies eligible based on inclusion criteria, citations/references were examined to retrieve relevant studies which may have been omitted in the initial Pub Med search criteria.

Inclusion criteria

Papers were considered eligible for inclusion if they fulfilled all of the following criteria:

- (1) Described clinical trials or mass treatment for lymphatic filariasis
- (2) Included clinical outcomes of hydrocele, lymphedema, or ADL
- (3) Full text of the article was available
- (4) The article was written in English

Assessment of methodological quality

In order to evaluate the quality of evidence and grade the strength of recommendations, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for rating evidence was employed [58]. Studies were

graded as High, Moderate, or Low quality (Low category including low and very low). Randomized control trials were considered high quality, but downgraded if influenced by the following:

- Limitations: lack of randomization, lack of blinding, large losses to follow-up, confounding, failure to report outcomes (if no effect observed).
- Inconsistent Results: differences in clinical assessment methods, interventions (drug dosages), or outcomes.
- Indirectness of evidence: drug to placebo compared to drug to placebo (lower quality) versus head to head comparisons (higher quality), differences between the population, intervention, comparator to the intervention and outcome of interest
- Imprecision: involving a small population and few events
- Publication bias

Observational studies (cohort, cross sectional survey) were considered low quality and graded up based on:

- Large magnitude of effect
- Plausible confounding, which would reduce a demonstrated effect
- Dose-response gradient

Data extraction

Data from each study were extracted including study type, sample size, clinical assessment, follow-up time and a consideration of limitations. Studies were scored as 'low, 'moderate' or 'high' quality based on the following criteria:

Quality Criteria	Low	Moderate	High
Study Type	Observational Studies	Based on criteria to upgrade or downgrade	Clinical Trials
Sample Size	≤30 is low	31-49	≥ 50
Clinical Assessment	Descriptive case definition with no standardized definition	Standardized definition and grading/staging (WHO, 0-4 scale)	Quantified assessment (measurements, volume displacement) or diagnostic tool (ultrasound, lymphoscintigraphy)
Follow up time	≤1 year	>1-4 years	>4 years
Limitations	≥ 5 limitations	4 limitations	≤ 3 limitations

Data synthesis

Given the heterogeneity between the studies in regards to methodological quality and outcome measures, statistical data pooling was not considered an option. Instead, strength of evidence and recommendations were based on GRADE rating as strong, moderate or weak [59].

The level of evidence was ranked and divided into the following levels:

1. Strong evidence: provided by quality assessment ≥3 high quality ratings
2. Moderate evidence: provided by at least 2 high quality ratings or one high-quality and two or more moderate quality ratings

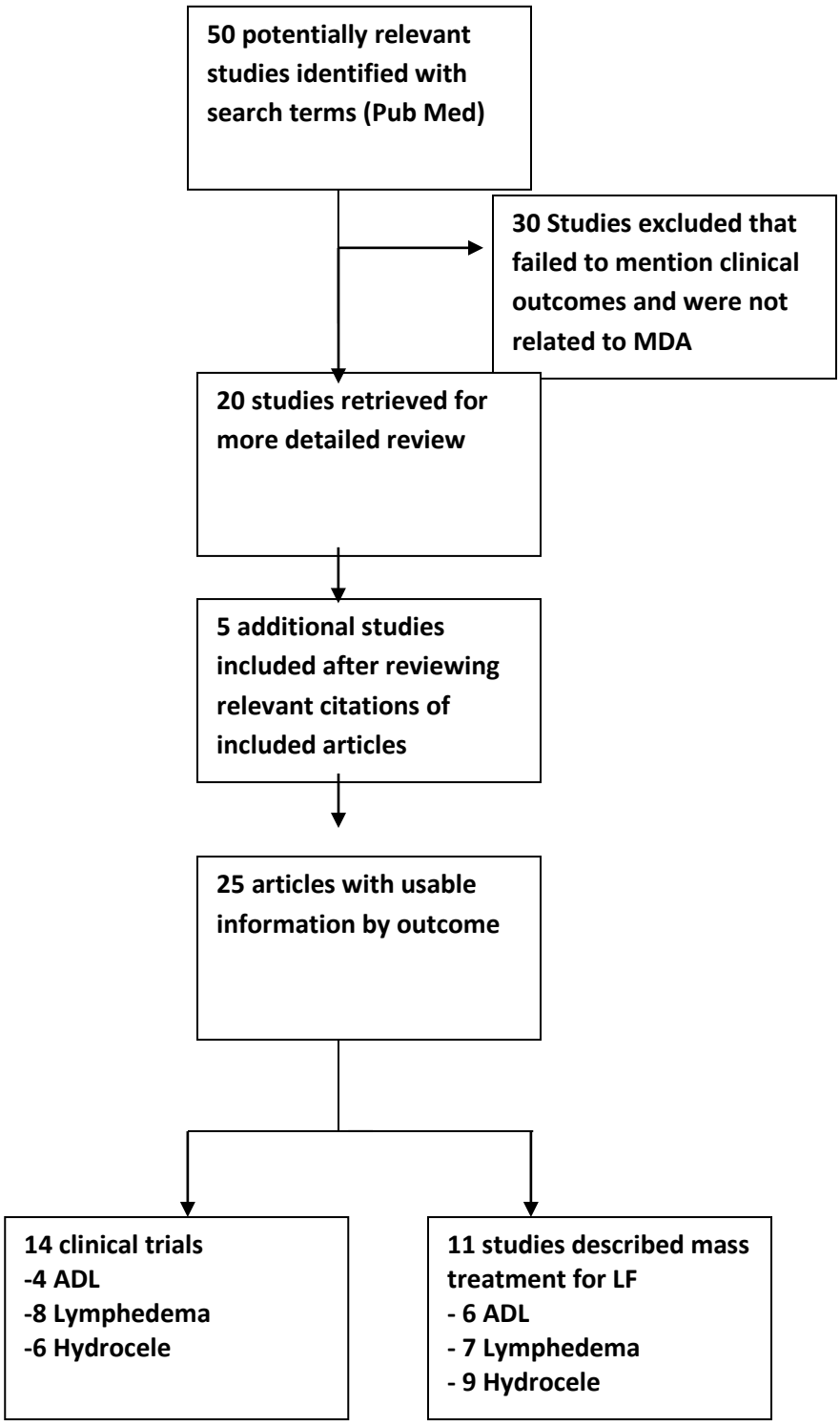
3. Limited or weak evidence: provided by ≥ 2 low-quality ratings with <2 high or ≥ 2 moderate ratings

IV. RESULTS

Eligible Studies

An initial search yielded 50 studies. Thirty studies were excluded which failed to mention clinical outcomes and were not directly related to MDA and morbidity; twenty studies remained. These studies were further assessed for any relevant publications that may have been missed by the initial search terms. After a thorough search of titles and abstracts from selected citations involving MDA and LF clinical disease, five additional studies met the inclusion criteria and were incorporated in this review. Thus, 25 total studies met the criteria for analysis (Table 1). Of these, ten evaluated ADL events, 15 assessed lymphedema, and 15 assessed hydrocele outcomes. Study design included 14 clinical trials and eleven prospective cohort, case study, or cross sectional evaluations. Of the clinical trials, ADL outcomes were considered in four [24, 30, 39, 41], lymphedema in eight [30, 41, 51, 60-64], and hydrocele in six [41, 62-66]; of other study designs assessing clinical outcomes after MDA, six assessed ADL [36, 40, 42-44, 67], seven lymphedema [35, 36, 42-44, 68, 69] and nine hydrocele [35, 36, 42, 44, 68, 70-73].

Figure 2: Flow Diagram of studies selected for review



Description of Eligible Studies

In the analyses of MDA on ADL, lymphedema and/or hydrocele outcomes, studies most commonly reported changes in prevalence, incidence, and/or percent difference of clinical manifestations over time. Follow up times ranged from a few months to 19 years with variable timing of clinical assessments including daily, monthly, and yearly intervals. A vast majority of studies evaluated DEC alone, 19/25 or 76% of included studies [24, 30, 36, 40-44, 51, 60-62, 65, 68-73]. Three additional studies evaluated the effects of combination therapy with DEC and abendazole or ivermectin alone [35, 39, 66] and head to head comparisons of ivermectin and DEC [64] as well as ivermectin and abendazole [63]. Early studies (1949 to 1957) evaluated a range of dosing of DEC on microfilaremia, but the majority of studies looked at MDA dosing of DEC at 6 mg/kg body weight [30, 35, 36, 39, 40, 44, 61, 62, 66, 69, 70, 72]. Nevertheless, dosing schedules for DEC in these studies varied considerably: monthly doses for one year [36, 40], daily doses for 12 days [30, 61, 62, 70], or a single annual dose [35, 39, 64, 72]. In addition, study populations ranged from a few clinical cases [51, 69, 70] to hundreds of cases [35, 36, 44, 61, 68].

Methodological quality

After an evaluation of study quality based on aforementioned criteria, six publications were found to offer strong evidence (Table 2 and 3) [24, 30, 35, 65, 66, 72]; nine studies were found to offer moderate evidence [36, 39, 43, 51, 61-64, 71]. In total, 15 studies were considered to be of sufficient quality for an in depth analysis.

Of the quality studies, five were an evaluation of MDA via prospective cohort design [35, 36, 43, 71, 72]; ten were clinical trial design with the strongest evidence represented mainly by clinical trials [24, 30, 39, 51, 61-66]. ADL was followed by five studies [24, 30, 36, 39, 43], lymphedema by nine [30, 35, 36, 43, 51, 61-64], and hydrocele by nine [35, 36, 62-66, 71, 72].

ADL Results

Overall, all five studies included based on moderate to high quality ratings reported a decrease in ADL over the course of the study period [24, 30, 36, 39, 43].

The clinical trials that showed improvement included Joseph, et al. (2004), Kerketta et al. (2005), and Tisch, et al.(2011) (Table 4). Joseph, et al. (2004), comparing the efficacies of affected-limb care with penicillin, DEC, the combination of both drugs or antibiotic ointment over twelve months, found a significant decrease in the mean incidence of attacks from 2.7 episodes per person-year in the pre-treatment year to 0.38 episodes per person-year ($P<.01$) during the treatment year. The mean incidence of attacks during treatment, 0.14 attacks per person-year, was lowest in the DEC-penicillin arm. Of note, the most considerable decrease on acute incidence was seen in 58 subjects who received penicillin with or without the addition of DEC. In this study, the addition of DEC to penicillin and limb care did not appear to offer additional benefits. Kerketta, et al. (2005), comparing DEC alone, oral penicillin and a topical antiseptic, found a significant reduction in ADL frequency after one year of treatment in all arms, with DEC treatment alone showing the least overall reduction. A foot care component was in place during the study. Tisch, et al. (2011), reported a decrease of acute attack incidence from

.39 per person-year to .20 ($p < 0.0001$) at the end of four annual treatments of DEC alone when compared to DEC and ivermectin as a single annual dose. No significant difference in the risk of acute filarial morbidity (AFM) was found to relate to drug regimen, but age, living in an area of high transmission, and chronic LF pathology were found to significantly contribute to ADL occurrence. All clinical studies accounted for a reduction of ADL events. However, it is important to note that both Joseph, et al. (2004), and Kerketta, et al. (2005), conducted studies after the implementation of WHO recommendations to include hygiene education in LF elimination programs, whereas Tisch, et al. (2011), evaluated ADL events before recommendations were in place.

Epidemiological studies that showed improvement of ADL included studies conducted by March, et al. (1960), and Partono, et al (1989) (Table 5). March, et al. (1960), surveying males above the age of 20 who received DEC through mass administration, reported a decrease in the prevalence of acute filarial lymphangitis attacks from 36.0% to 4.0% after ten years. No effort was made to include the same persons in the second survey that were examined in the first survey. Partono, et al. (1989), in an investigation of a *B. timori* endemic area receiving DEC for eleven years, found a decline in the ADL rate from 46% to 11%. Although reporting an overall reduction in ADL prevalence over the course of the investigation, the same study also recognized the incidence of new cases reflecting either an inadequate response to drug therapy or the result of uninterrupted transmission of microfilariae.

Lymphedema Results

From included studies assessing lymphedema and/or elephantiasis, improvement was noted in five studies [30, 35, 36, 43, 61] and a lack of improvement was noted in the remaining four [51, 62-64].

The clinical trials that showed improvement included three studies [30, 35, 43] (Table 4). Pani, et al. (1989), evaluating the effect of DEC on 103 patients with recent edema (RO) and 132 patients with persistent edema (PO) using DEC, found 85% of RO patients and 77% of PO patients demonstrating either regression or no change. Regression of edema occurred in 70% of RO cases, 52% of PO cases without skin changes and 36% of PO cases with skin changes. Children less than ten years old experienced near total regression. The degree of edema regression was significant by the number of DEC courses, up to five courses of DEC, in RO cases only. Findings showed that DEC, with other supportive therapy, can result in a significant reduction in edema volume with more evidence of regression in those with recent versus advanced persistent disease. Supportive therapy in this study involved offering patients with ADL anti-inflammatory medications and antibiotics, offering patients with pitting edema a diuretic at the first visit, and offering all patients crepe bandages and instruction. Difference in adherence to edema management was not reported. With these measures offered to all patients, it is difficult to determine the direct effects of DEC. Bockarie, et al. (2002), comparing DEC and ivermectin with DEC alone, reported a lymphedema pre-trial prevalence of 5% and a prevalence of 4% after four rounds of MDA treatment; however a cohort sub-study of persons who entered the study with lymphedema revealed a reduction

of 69%. Despite such a large reduction, the minimal change in disease prevalence may suggest an incidence of new-onset lymphedema. Kerketta, et al. (2005), comparing penicillin, DEC and topical antiseptic regimens, found a significant decrease in leg circumference following exposure to DEC, but did not take into account the involvement of a confounding foot care component and failed to account for the correlation among individuals.

The clinical trials that showed a lack of improvement included four studies [51, 62-64]. Meyrowitsch, et al. (1996), comparing DEC in the standard dose of 6 mg/kg x 12 days with DEC over two treatments every six months, discovered that out of 17 cases of leg elephantiasis, 13 remained unchanged, one progressed to a more advanced stage, two reduced to an earlier stage, and one exhibited complete disappearance. A major limitation of this evaluation was the small number of cases included, limiting the ability to determine a clear effect based on an adequate sample size. Dunyo, et al.(2000), comparing ivermectin alone, albendazole alone, both in combination, and placebo, reported that of 48 lymphedema patients, nine experienced a reduction in grade or disappearance and three experienced an increase in grade twelve months post treatment. Low numbers of cases did not allow statistical analysis of the data. Das, et al.(2003), in a clinical trial comparing Daflon 500 mg and DEC 25 mg BID x 90 days with DEC 25 mg alone, reported a percentage change in 26 patients with lymphedema as 29.1% in the Daflon and DEC group and no change in the DEC group at the end of treatment period, and 63.8% and 9%, respectively, at the end of the follow-up period. Measurements of lymphedema via water displacement method were not defined and the study was limited to a few patients. Yuvaraj, et al. (2008), found that the lymphedema/elephantiasis

prevalence declined only marginally and without statistical significance from 3.7% to 3.2%, 4.6% to 3.9% and 2.9% to 2.3% in the DEC, ivermectin, and placebo arms.

Epidemiological studies that showed improvement included two studies (Table 5) [36, 43]. March, et al. (1960), reported notable spontaneous regression of early elephantiasis occurring after DEC. Of 2689 persons examined, 2.1% were found to have elephantiasis in 1949 whereas only 0.2%, were found positive in 1959. In the group above 20 years of age, elephantiasis was reduced 60%, from 13.2% to 5.0% and no elephantiasis was noted in those under age 20. Additionally, no new cases of lymphedema/elephantiasis developed in anyone receiving DEC. A major limitation of the study involved the following of a cohort rather than the following of individual cases over the study period. Without knowing the course of specific clinical disease, it is impossible to know how DEC directly influenced case outcomes and if prevalence data simply reflected the death of cases rather than morbidity improvement. Partono, et al. (1989), found DEC, given as a ten day course twice a year followed by four years of selective treatment, has a positive long-term effect on lymphedema elephantiasis, especially in the less developed forms of the disease before the onset of fibrosis. Three-fourths of patients with elephantiasis in 1977 had resolved by 1980 and remained in that condition; the remaining 25% appeared intractable, even when exposed to long-term DEC therapy.

Hydrocele Results

The data regarding hydrocele remains divided. Hydrocele was found to improve in five studies [35, 36, 62, 64, 71], whereas no improvement was recorded in four [63, 65, 66, 72].

The clinical trials that showed improvement included three studies (Table 4) [35, 62, 64]. Meyrowitsch, et al., in 1996 reported that one year after the start of treatment, 76.9% and 62.5% of males who had hydroceles during the pre-treatment survey in two separate groups, respectively, showed improvements. One year after the start of treatment, no new cases of hydrocele had developed in males in the control group, and only one new case of hydrocele appeared in the treatment group. At a four year follow-up investigation in 1998, Meyrowitsch, et al., continued to evaluate chronic hydrocele from the original pre-treatment survey, and discovered that 23% of overall subjects presented at a more advanced stage of hydrocele, whereas regression or complete disappearance was seen in 44%. Bockarie, et al. (2002), reported a pre-trial hydrocele prevalence of 15%, a post-trial prevalence of 5%, and an 87% reduction in a subgroup of hydrocele patients after four MDA treatments. Yuvaraj, et al. (2008), after seven rounds of DEC and ivermectin MDA, reported a decline in hydrocele prevalence from 20.5 to 5.1% ($P < 0.05$) in the DEC arm, 23.9% to 10.4% ($P < 0.05$) in the ivermectin arm, and 20.4% to 10.9% ($P < 0.05$) in the placebo arm, demonstrating reductions of 75.3%, 56.6% and 46.6%, respectively. Ages 0-20 were free of hydrocele.

The clinical trials that showed improvement included four studies [63, 65, 66, 72]. Dunyo, et al. (2000), comparing ivermectin alone, albendazole alone, and in combination, found a reduction or disappearance of hydrocele in 14 of 37 cases, one case of hydrocele

enlargement and five new cases. Treatment was found not to influence clinical manifestations. Bernhard, et al.(2001), related a statistically significant reduction in scrotal size in the DEC group after 3 months ($p < 0.0001$) and 6 months ($p= 0.02$) but not after 12 months, and reported no statistically significant difference between DEC and placebo at any of the time points for either hydrocele fluid volume or scrotal size. Using ultrasound to detect cases, the study reported difficulty estimating large hydroceles and only included a few individuals with small hydroceles. Noroes, et al. (2003), also using ultrasound examination, found that 40 (22.3%) men experienced acute hydrocele after treatment with DEC. Acute hydrocele occurred more frequently in men who received DEC (26.5%) than in those who developed spontaneous intrascrotal nodules (10.6%, $p= 0.03$).

Men who developed hydrocele were significantly more likely to have received DEC (87.5%) than those who did not develop hydrocele (69.8%, $p= 0.03$). Nine (5.1%) men developed hydrocele that either did not resolve within the 18 months or continued to increase in size during the follow-up period, and 28 (75.7%) had hydroceles that resolved spontaneously. Only the presence of multiple nodules remained significantly associated with hydrocele ($p= 0.01$); DEC treatment was of borderline significance ($p= 0.051$). Ultrasound technician user error and experience were noted as possible limitations to the study. Hussein et al. (2004), from ultrasound reports derived from a trial comparing single dose DEC and albendazole with seven daily doses, found motile filarial worms, before therapy, in 28 of 36 men (78%). Subclinical hydroceles and intrascrotal calcifications were increased after treatment in both groups, but both of these parameters returned toward pre-treatment levels at later time points. No significant difference was

discovered in the rates of development of hydroceles or calcifications between the two treatment groups. As a limitation, the study was restricted to clinically normal subjects.

The only epidemiological study to follow hydrocele, March, et al. (1960), found that for males above 20 years of age, hydrocele prevalence decreased from 9.8% in 1949 to 3.2% in 1959. No new cases of hydrocele were found. As stated, the study reported the prevalence of cases without following individual patients with clinical disease.

V. DISCUSSION

Issues with Study Design

A dearth of high quality evaluations based on study design alone has made it possible to produce and perpetuate data with conflicting and indeterminate results related to LF morbidity. As late as 2001, studies on MDA and clinical disease have failed to employ high quality randomized, blinded, placebo-controlled trials. In studies prior to 1990, no controls were used in clinical trials secondary to ethical considerations [43, 61]. Bernhard, et al.(2001), pointed to the fact that, in the absence of a control comparison, daily fluctuations in scrotal size secondary to external changes in factors like ambient temperature, work load and type, and nutritional status can be incorrectly attributed to MDA; similar and uncontrollable fluctuations are known to occur in lymphedema patients as well [50, 65]. Additionally, studies have been underpowered in case numbers and have been unable follow the same cases directly for a long enough period of time to give credibility to results.

Issues with Clinical Definitions

Studies on MDA and clinical disease have employed vague terminology in clinical determination terminology (Table 6). This has inevitably affected results and led to a misclassification of clinical disease outcome.

Early studies recorded a history of ADL and documented evidence of clinical findings without outlining how these findings differed from non-filarial sources of infection [40-42, 60]. Only one study noted the exclusion of lymphangitis caused by

recent bacterial infection into a non-filarial category [36]. In contrast, no attempt was made by a recent investigation to differentiate the derivation of self-reported extremity swelling accompanied by fever [39]. It was unknown if the swelling and fever resulted from a previous injury or from a secondary bacterial infection, and thus unclear if the outcome truly represented an ADL event. The same study also acknowledged malaria as a potential cause of incorrect categorization of outcome. A component of ADL, filarial fever, is defined as a severe recurrent fever with headache, malaise, chills, and rigors, which can closely resemble malaria [23]. Although usually accompanied by other early signs of filariasis, ADL symptoms may manifest as fever alone. Four of seven studies evaluating acute events mention malaria as endemic to the study site [39, 40, 42, 43]. According to Partono, et al. (1989), despite study districts being endemic to four species of human malaria, adequate control of filariasis was achieved in the absence of any attempt to decrease the mosquito population [43]. Although a positive finding in favor of MDA, the study failed to mention how malaria and malarial control may influence LF classification. Areas native to diseases such as malaria and prone to secondary bacterial infections may cause researchers or subjects to misclassify ADL events and thus skew resulting prevalence and incidence data. This is most important when relying on methods such as self-reporting and timing of clinical assessments to reduce overall bias.

In the case of lymphedema, many authors have utilized the term elephantiasis for all forms of limb enlargement and swelling [36, 40, 43], whereas lymphedema and elephantiasis were considered separate manifestations in other assessments [44]. These conflicting definitions add confusion to results and obfuscate comparisons. Additionally, co-morbidities such as venous disease prevalence have been known to influence case

diagnosis and definition. Before ascribing all unilateral lymphedema cases as filarial, Das, et al., excluded conditions including venous insufficiency and varicose ulcers after taking a careful history and performing a thorough clinical examination [51]. In an analysis of the filariasis control program in Samoa, Ciferri, et al. (1969), made a point to include those with unequivocal signs of elephantiasis in the final data presentation, excluding borderline or minor cases of elephantiasis of the limbs, genitalia, and breasts [44]. Unfortunately, there is no follow up explanation on what borderline cases may represent. Despite the effort to conduct thorough clinical evaluations of lymphedema patients, confounding conditions remain undocumented and unknown in several of the areas under investigation. Ultimately, it is necessary to differentiate concomitant conditions in order to prevent misclassification and ensure accurate reporting.

Issues with Confounding

As recommended by the World Health Organization, LF programs are currently encouraged to introduce disability alleviation services, as well as hydrocelectomy surgical programs, to reduce overall morbidity [3, 50]. Hygiene and skin care regimens have been found to be extremely effective in those suffering from chronic lymphedema [50]. Joseph, et al.(2004), recommended this intervention as the primary therapeutic measure for diminishing lymphedema morbidity and ADL attacks due to its affordability and ease of delivery [24]. Interventions such as leg elevation, bandaging, diuretics, massage, and antibiotic ointment treatments impair the ability of studies to assess lymphedema reduction and disease regression as attributable to MDA therapy alone. Most studies evaluating hydrocele have controlled for hydrocelectomy procedures by excluding participants with a surgical history [66, 70, 72]. It remains important to

consider surgical procedures as a potential confounder when evaluating hydrocele and lymphedema resolution after MDA. Although the direct impact of MDA on chronic disease is confounded by these measures, it is still possible to evaluate MDA impact by monitoring for the incidence of chronic disease.

Issues with Clinical Assessment

The studies included in this systematic review revealed significant variability with clinical assessment. In ten experimental areas on the islands of Tahiti and Maiao, subjects received a brief physical examination by the senior author before DEC administration and at six and twelve months [42]. During the investigation period, lymphangitis attacks were recorded monthly. Further studies employed various tools such as clinical survey [36, 40, 44], to record a history of acute attacks, and monitored clinical results at a variety of selected times: before treatment, annually during treatment, and after treatment [40], at yearly follow up [43], and via weekly active surveillance [39]. Overall, studies have been incongruent in their approach, but have generally employed a physical examination and survey assessment as a means to secondarily gage clinical response to MDA administration with the primary priority of determining drug efficacy, tolerance, side effects, and hematological outcomes. Minimal studies have examined reduction in acute filariasis morbidity as a main endpoint. Future studies should consider focusing MDA studies on clinical outcomes with regular follow up times and a standardized approach with the goal of understanding best practices to control clinical morbidity.

Outcome assessments of lymphedema, elephantiasis, and hydrocele have utilized undefined, poorly defined, or confusing physical examination classification or grading

methods (Table 6). A wide variety of lymphedema and hydrocele monitoring techniques have included employing measurements at defined points such as the lower limbs, water displacement, visual assessment by study staff, WHO recommended staging, and technologies including ultrasound and lymphoscintigraphy. Most research to date on MDA and filarial lymphedema has used either a three or four stage system of classification. These limited categories have been confusing to researchers in the past due to the difficulty of choosing between borderline clinical manifestations, and have thus led to the potential misclassification of disease severity on initial examination and at follow-up, especially if recorded at both points by two separate researchers. This issue has led to increasing acceptance of the seven stage system developed by Dreyer, et al., for lymphedema assessment [50, 74]. Dreyer staging employs a system with well-defined categories based on obvious features of clinical disease rather than measures of leg volume or a subjective judgment of severity. However, due to variability within stages, leg circumference has been found to be preferable to other researchers. It has also been argued that leg circumference is not the best way to gauge lymphedema progression because it is variable depending on time of day, amount of time a person spends on one's feet and the female monthly hormonal cycle [50].

Issues with clinical follow up

While assessing the role of MDA's influence on ADL, many studies have only evaluated the effect of drug treatment in persons with existing morbidity. This is often understandable given study follow up times ranging from a few months to a few years. In the case of hydrocele or lymphedema, it may prove difficult to secure the funding and human resources needed to follow the incidence of chronic disease. Beye, et al. (1952),

recorded clinical filariasis in 41% of persons examined over one year of age and recent advances in diagnosis have confirmed that LF infection often occurs in childhood [33, 42]. In a table outlining the percentages of male Tahitians with clinical manifestations of filariasis, researchers discovered that by age 50, 61.2% of participants reported a history of lymphangitis, and Simonsen, et al. (1995), following hydrocele manifestations, found an increased prevalence with age, up to 52.9% in males 45 years or older [40, 42, 70]. Given these circumstances when considering the utilization of clinical manifestations of LF to evaluate MDA administration, ADL may prove a more viable way to track the incidence of cases and gage program success over the short term.

Summary of effect of DEC on filarial morbidity

Studies following the clinical course of MDA have involved DEC with or without the addition of ivermectin or abendazole. A wide range of studies have looked at DEC alone, in combination, as a medicated salt and at a range of dosing intervals and amounts. It has been difficult to select the best option for DEC administration, despite its long use, based on a history of incongruent study designs, diagnostic techniques, and evalution criteria [70]. Most mass administration chemotherapy experience has been with DEC, despite its undetermined role in the management of morbidity. It is not only important to understand DEC's impact from a clinical standpoint, but also from a financial one. While ivermectin and albendazole are donated, DEC is not. This financially strains program budgets, and limits quality control over the drug itself since there is no current standard distribution arrangement for DEC procurement [3].

DEC alone has been found to decrease the incidence and frequency of ADL attacks, but many of the studies reporting clinical improvement have failed to follow

incidence in the same clinical cases and were conducted in the context of a concurrent skin and hygiene management program. These factors obscure the impact of DEC and make conclusions on its direct impact on ADL negligible.

The data regarding DEC and lymphedema is mixed with more studies demonstrating improvement than not. Previous studies have mostly evaluated the effectiveness of DEC against microfilarie as a result of its microfilaricidal properties, and the mechanism of edema regression following therapy with DEC remains unknown [61, 75]. It is thought that the pathology of lymphedema occurs as the result of disruption of the lymphatic channels by adult worms, and the disturbance of DEC on adult worm burden can lead to edema regression. In one study, repeated application of DEC was found to have a profound influence with long-term administration, showing significant alleviation and reversal of chronic disease including lymphedema and pre-fibrotic elephantiasis [43]. In contrast, Pani, et al.(1989), reported a poor response and an increase in edema in 45 patients after treatment with DEC [61]. Currently there exists no technique available to measure the mechanism behind why this occurs. Additionally, data are inconsistent and limited in terms of understanding the significance of studies reporting lymphedema reduction after DEC.

Hydrocele results are varied regarding improvement after MDA. Studies have shown that mass treatment with DEC may reduce overall hydrocele prevalence and cause a reduction in the size of smaller hydroceles [35, 62, 70]. Smaller hydroceles in these studies were defined as six to eight centimeters in size [62, 70]. The total duration of these smaller hydroceles remains unknown, but the mechanism behind their resolution may involve the pathogenesis of acute hydrocele as described by Noroes, et al. (2004)

[72]. Acute hydrocele is thought to derive from treatment with DEC, the death of W. bancrofti, and with the formation of multiple granulomas in the superior paratesticular lymphatic vessels. The presence of multiple granulomas, in turn, contributes to the obstruction of lymphatic vessels and lymphangiectasia . After the reabsorption of granulomas, lymphatic vessels are able to recanalize, and the subsequent restoration of lymphatic flow can result in the spontaneous resolution of acute hydrocele. If this defines the progression of acute or smaller hydroceles, then the natural clinical disease course of granuloma reabsorption may contribute to the underlying reason behind resolution, rather than DEC alone.

Summary of effect of ivermectin and albendazole on filarial morbidity

Three additional studies evaluated the effects of combination therapy with DEC and abendazole or ivermectin alone [35, 39, 66] and head to head comparisons of ivermectin and DEC [64] as well as ivermectin and abendazole [63]. There is a paucity of data regarding the direct effect of ivermectin and albendazole on clinical morbidity since most studies have mostly involved these drugs in combination with DEC. Hussein, et al.(2004), reported the intensification and development of both subclinical and palpable hydrocele following treatment with DEC in combination with albendazole [66]. It remains to be determined if the combination of DEC and albendazole contributes to hydrocele progression more or less than DEC alone. Bockarie (2002) and Tisch (2011), et al., found no significant difference related to a drug regimen of DEC alone versus DEC in combination with ivermectin with an overall reduction of morbidity witnessed in both studies.

A direct head to head comparison of ivermectin and albendazole conducted by Dunyo, et al. (2000), found no significant effect of treatment on clinical manifestations. The only head to head comparison of DEC and ivermectin by Yuvaraj, et al. (2008), found that lymphedema/elephantiasis prevalence declined only marginally, but DEC was found to significantly reduce hydrocele prevalance, which was less evident in the ivermectin arm [64].

Without a general consensus or sound data to endorse any particular MDA regimen over another regarding morbidity, alternatives and additions to current MDA regimens should continue to be investigated. In a study by Das, et al. (2003), Daflon and DEC was found to reduce LF morbidity when compared to DEC alone [51]. Daflon is known to be safe, efficacious, and well tolerated, but the study did not evaluate a Daflon arm alone, so further research is needed to confirm its positive effect on LF morbidity.

V. RECOMMENDATIONS

Since the timeline of ADL typically occurs before the onset of hydrocele and lymphedema and recurrent ADL attacks are considered to be a main risk factor for their development, perhaps it is a more viable option to utilize first ADL attack as a more financially feasible endpoint in shorter term assessments of morbidity than waiting for LF's long-term phenotypes, or to limit study designs to the evaluation of hydrocele and lymphedema in older patients where prevalence studies have revealed a higher number of available and emerging cases. As previously stated, follow-up times have been variable and are dependent on the outcome being measured. ADL requires a vigilant approach in order to avoid missing transient attacks and relying on self-reporting of events, whereas the assessment of hydrocele or lymphedema can be monitored on a less regular basis. Ideally, trained staff would monitor ADL patients every week and hydrocele and lymphedema chronic cases on at least a monthly basis. In the future, it may prove important to also consider response to therapy based on the timing of MDA treatment, age of participants, duration of edema, and initial volume [61].

Clinical observations might also achieve better reliability with the use of examinations performed by more consistent and standardized ultrasonography, lymphscintigraphic, and tonometry technologies. In a study conducted by Shenoy, et al. (2009), an evaluation of children, using both ultrasonography and lymphoscintography, with subclinical disease after MDA exposure demonstrated reversibility of lymphatic damage [33]. Monitoring morbidity may be achievable and justifiable if such tools are available to track similar physiologic changes in chronic disease cases after mass drug intervention.

Lymphoscintigraphic studies have shown evidence of dilated dysfunctional lymphatics attributable to the manifestation of morbidity in individuals susceptible to clinical disease [13, 14]. Freedman, et al., using lymposcintigraphy, did not observe any improvement in lymphatic pathology after two courses of DEC (for 12 days each) in lymphedema cases [13, 69]. A case report presented by Moore, et al. (1996), looked at acute lymphatic dysfunction via TC-lymphoscintography within three months of infection in a Peace Corps volunteer. Results from the patient displayed enhanced lymphatic flow in the affected leg, a common finding in lymphatic dysfunction. After receiving three 6 mg/kg doses of DEC for 21 days, both legs were symmetrical and without evidence of disease one week after completion of DEC treatment. Repeat lymphoscintography confirmed restoration of normal lymphatic flow. In the end, the issue involved with clinical assessment of lymphatic dysfunction and lymphedema lies with detection, and utilizing a standardized tool will add reliability to results.

Lymphoscintigraphy has been established as an effective method for uncovering subtle lymphatic changes, but its employment in monitoring clinical cases requires the use of facility and staff available to handle the injection of radioactive dye [76]. This limits its use in the field and adds risk in terms of properly addressing potential contradictions to the procedure. Tonometry has been proposed as a simple and portable tool which allows for a non-invasive measure of the skin and tissue's ability to resist compression. In a study by Gordon, et al. (2011), mean tonometric measurements of selected sites were found to be significantly higher in patients with LF compared to those without LF demonstrating the ability of the test to detect differences in subclinical disease [76]. Further analysis revealed an optimal cut-off of 3.5 with 100% sensitivity

which could be used to screen young individuals living in endemic areas, help focus morbidity management strategies at an earlier and more effective time, and monitor disease progression. However, further research is needed in more diverse populations to assure the validity of the measurement device.

Another advanced tool in the assessment of LF morbidity, ultrasound examination is now a well-established procedure used to detect the presence of living adult worms and assess the anti-adult activity of antifilarial drugs [16, 32, 72]. Most studies have used ultrasound to evaluate the pathophysiology and changes specific to hydrocele. In terms of selecting patients for ultrasonographic assessment, presence of scrotal pain or report of a feeling of increased volume should not be used in selection criteria since most men with hydrocele do not recall pain, inflammatory episodes, or changes in scrotal volume as triggering events [72]. Rather, studies should focus evaluations on physical exam studies of nodule palpation and ultrasound exams to assess efficacy of MDA to better utilize time and resources.

VI. CONCLUSION

The mixed results of this review stress the need to provide more standardized data to better understand the course of clinical disease after MDA implementation . Correct clinical determination and evaluation of ADL, lymphedema, and hydrocele depends on a consistent methodology of data collection and reporting of outcomes. As evidenced by the diversity of monitoring techniques from the studies included in this systematic review, there is not a systematic approach to the evaluation of LF morbidity. Studies on MDA and clinical disease demonstrate numerous inconsistencies related to the source of clinical data (program physicians, researchers, trained locals, self-report from study participants), follow up times (weeks, months, years), study type (cross sectional, prospective cohort, clinical trial), study population (men only, adults only, all ages), drug type, dosing and dosing schedules. These inconsistencies make direct comparisons difficult to interpret and to analyze, and may represent the underlying reason for such a wide range of conflicting results describing the influence of MDA on clinical outcomes, especially in regards to lymphedema and hydrocele. In the end, studying morbidity reduction as a result of the efforts of GPELF will help to justify existing program efforts and clarify the need to introduce new efforts when needed. Monitoring morbidity with rigorous methodology is essential in understanding and responding to the course of filarial disease, a disease with long-term significance. Determining the incidence of cases and following a regimented follow-up schedule of clinical outcomes, with standardized diagnostic tools, in a newly established program, would ideally set the stage to feasibly determine MDA efficacy.

REFERENCES

1. *Global Programme to Eliminate Lymphatic Filariasis: progress report on mass drug administration in 2009*, in *Weekly Epidemiological Record, 2010*2009. p. 365-372.
2. *Global Programme to eliminate lymphatic filariasis: progress report on mass drug administration, 2010.* Wkly Epidemiol Rec, 2011. **86**(35): p. 377-88.
3. World Health Organization, *Progress Report 2000-2009 and Strategic Plan 2010-2020*, in *World Health Organization Global Programme to Eliminate Lymphatic Filariasis* 2010.
4. Addiss, D.G. and M.A. Brady, *Morbidity management in the Global Programme to Eliminate Lymphatic Filariasis: a review of the scientific literature.* Filaria J, 2007. **6**: p. 2.
5. Wynd, S., et al., *Understanding the community impact of lymphatic filariasis: a review of the sociocultural literature.* Bull World Health Organ, 2007. **85**(6): p. 493-8.
6. Grady, C.A., et al., *Endpoints for lymphatic filariasis programs.* Emerg Infect Dis, 2007. **13**(4): p. 608-10.
7. Dreyer, G., et al., *Pathogenesis of lymphatic disease in bancroftian filariasis: a clinical perspective.* Parasitol Today, 2000. **16**(12): p. 544-8.
8. Center for Disease Control and Prevention. *Life Cycle of Wucheria bancrofti*. October, 2011]; Available from: http://www.dpd.cdc.gov/dpdx/HTML/Frames/A-F/Filariasis/body_Filariasis_w_bancrofti.htm
9. The Carter Center. *Lymphatic Filariasis Elimination Program*. Available from: http://www.cartercenter.org/health/lf/index.html
10. World Health Organization. *Lymphatic Filariasis*. October, 2011]; Available from: http://www.who.int/lymphatic_filariasis/epidemiology/en/.
11. Ramesh Narula, S.S., V.K Agarwal, Kusum Narula, *Brief Case History and Literature Review: Lymphatic Filariasis.* NJIRM, 2010. **1**(3).
12. Mand, S., et al., *The role of ultrasonography in the differentiation of the various types of filaricele due to bancroftian filariasis.* Acta Trop, 2011. **120 Suppl 1**: p. S23-32.
13. Freedman, D.O., et al., *Lymphoscintigraphic analysis of lymphatic abnormalities in symptomatic and asymptomatic human filariasis.* J Infect Dis, 1994. **170**(4): p. 927-33.
14. Shenoy, R.K., et al., *Lymphoscintigraphic evidence of lymph vessel dilation in the limbs of children with Brugia malayi infection.* J Commun Dis, 2008. **40**(2): p. 91-100.
15. Rocha, A., et al., *Circulating filarial antigen in the hydrocele fluid from individuals living in a bancroftian filariasis area - Recife, Brazil: detected by the monoclonal antibody Og4C3-assay.* Mem Inst Oswaldo Cruz, 2004. **99**(1): p. 101-5.
16. Noroes, J., J. Figueredo-Silva, and G. Dreyer, *Intrascrotal nodules in adult men as a marker for filarial granuloma in a bancroftian filariasis-endemic area.* Am J Trop Med Hyg, 2009. **81**(2): p. 317-21.
17. *Recommendations of the International Task Force for Disease Eradication*, in *Morbidity and Mortality Weekly Report Recommendations and Reports*1993. p. 1-38.
18. Farid, H.A., et al., *A critical appraisal of molecular xenomonitoring as a tool for assessing progress toward elimination of Lymphatic Filariasis.* Am J Trop Med Hyg, 2007. **77**(4): p. 593-600.
19. Pani, S., et al., *Tolerability and efficacy of single dose albendazole, diethylcarbamazine citrate (DEC) or co-administration of albendazole with DEC in the clearance of Wuchereria bancrofti in asymptomatic microfilaraemic volunteers in Pondicherry, South India: a hospital-based study.* Filaria J, 2002. **1**(1): p. 1.

20. Ottesen, E.A., M.M. Ismail, and J. Horton, *The role of albendazole in programmes to eliminate lymphatic filariasis.* Parasitol Today, 1999. **15**(9): p. 382-6.
21. Noroes, J. and G. Dreyer, *A mechanism for chronic filarial hydrocele with implications for its surgical repair.* PLoS Negl Trop Dis, 2010. **4**(6): p. e695.
22. Addiss, D.G., et al., *Feasibility and effectiveness of basic lymphedema management in Leogane, Haiti, an area endemic for bancroftian filariasis.* PLoS Negl Trop Dis, 2010. **4**(4): p. e668.
23. Babu, B.V., A.N. Nayak, and K. Dhal, *Epidemiology of episodic adenolymphangitis: a longitudinal prospective surveillance among a rural community endemic for bancroftian filariasis in coastal Orissa, India.* BMC Public Health, 2005. **5**: p. 50.
24. Joseph, A., et al., *The efficacies of affected-limb care with penicillin diethylcarbamazine, the combination of both drugs or antibiotic ointment, in the prevention of acute adenolymphangitis during bancroftian filariasis.* Ann Trop Med Parasitol, 2004. **98**(7): p. 685-96.
25. Wijesinghe, R.S., et al., *Efficacy of a limb-care regime in preventing acute adenolymphangitis in patients with lymphoedema caused by bancroftian filariasis, in Colombo, Sri Lanka.* Ann Trop Med Parasitol, 2007. **101**(6): p. 487-97.
26. Debrah, A.Y., et al., *Doxycycline reduces plasma VEGF-C/sVEGFR-3 and improves pathology in lymphatic filariasis.* PLoS Pathog, 2006. **2**(9): p. e92.
27. Shenoy, R.K., et al., *A double-blind, placebo-controlled study of the efficacy of oral penicillin, diethylcarbamazine or local treatment of the affected limb in preventing acute adenolymphangitis in lymphoedema caused by brugian filariasis.* Ann Trop Med Parasitol, 1999. **93**(4): p. 367-77.
28. Suma, T.K., R.K. Shenoy, and V. Kumaraswami, *Efficacy and sustainability of a footcare programme in preventing acute attacks of adenolymphangitis in Brugian filariasis.* Trop Med Int Health, 2002. **7**(9): p. 763-6.
29. McPherson, T., et al., *Interdigital lesions and frequency of acute dermatolymphangioadenitis in lymphoedema in a filariasis-endemic area.* Br J Dermatol, 2006. **154**(5): p. 933-41.
30. Kerketta, A.S., et al., *A randomized clinical trial to compare the efficacy of three treatment regimens along with footcare in the morbidity management of filarial lymphoedema.* Trop Med Int Health, 2005. **10**(7): p. 698-705.
31. Dreyer, G., et al., *Bancroftian filariasis in a paediatric population: an ultrasonographic study.* Trans R Soc Trop Med Hyg, 1999. **93**(6): p. 633-6.
32. Fox, L.M., et al., *Ultrasonographic examination of Haitian children with lymphatic filariasis: a longitudinal assessment in the context of antifilarial drug treatment.* Am J Trop Med Hyg, 2005. **72**(5): p. 642-8.
33. Shenoy, R.K., et al., *Antifilarial drugs, in the doses employed in mass drug administrations by the Global Programme to Eliminate Lymphatic Filariasis, reverse lymphatic pathology in children with Brugia malayi infection.* Ann Trop Med Parasitol, 2009. **103**(3): p. 235-47.
34. Cantey, P.T., et al., *Increasing compliance with mass drug administration programs for lymphatic filariasis in India through education and lymphedema management programs.* PLoS Negl Trop Dis, 2010. **4**(6): p. e728.
35. Bockarie, M.J., et al., *Mass treatment to eliminate filariasis in Papua New Guinea.* N Engl J Med, 2002. **347**(23): p. 1841-8.
36. March, H.N., et al., *Reduction in the prevalence of clinical filariasis in Tahiti following adoption of a control program.* Am J Trop Med Hyg, 1960. **9**: p. 180-4.

37. Perera, M., et al., *Neglected patients with a neglected disease? A qualitative study of lymphatic filariasis.* PLoS Negl Trop Dis, 2007. **1**(2): p. e128.
38. Jullien, P., et al., *Efficacy of home-based lymphoedema management in reducing acute attacks in subjects with lymphatic filariasis in Burkina Faso.* Acta Trop, 2011. **120 Suppl 1**: p. S55-61.
39. Tisch, D.J., et al., *Reduction in acute filariasis morbidity during a mass drug administration trial to eliminate lymphatic filariasis in Papua New Guinea.* PLoS Negl Trop Dis, 2011. **5**(7): p. e1241.
40. Kessel, J.F., *An effective programme for the control of filariasis in Tahiti.* Bull World Health Organ, 1957. **16**(3): p. 633-64.
41. Hewitt, R., et al., *Follow-up observations on the treatment of bancroftian filariasis with hetrazan in British Guiana.* Am J Trop Med Hyg, 1950. **30**(2): p. 217-37.
42. Beye, H.K., et al., *Preliminary observations on the prevalence, clinical manifestations and control of filariasis in the Society Islands.* Am J Trop Med Hyg, 1952. **1**(4): p. 637-61.
43. Partono, F., R.M. Maizels, and Purnomo, *Towards a filariasis-free community: evaluation of filariasis control over an eleven year period in Flores, Indonesia.* Trans R Soc Trop Med Hyg, 1989. **83**(6): p. 821-6.
44. Ciferri, F., et al., *A filariasis-control program in American Samoa.* Am J Trop Med Hyg, 1969. **18**(3): p. 369-78.
45. Chandrasena, T.G., et al., *Modified Dermatology Life Quality Index as a measure of quality of life in patients with filarial lymphoedema.* Trans R Soc Trop Med Hyg, 2007. **101**(3): p. 245-9.
46. Pani, S.P. and A. Srividya, *Clinical manifestations of bancroftian filariasis with special reference to lymphoedema grading.* Indian J Med Res, 1995. **102**: p. 114-8.
47. Ramaiah, K.D., et al., *Functional impairment caused by lymphatic filariasis in rural areas of south India.* Trop Med Int Health, 1997. **2**(9): p. 832-8.
48. Lammie, P.J., K.T. Cuenco, and G.A. Punkosdy, *The pathogenesis of filarial lymphedema: is it the worm or is it the host?* Ann N Y Acad Sci, 2002. **979**: p. 131-42; discussion 188-96.
49. Nutman, T.B., *Experimental infection of humans with filariae.* Rev Infect Dis, 1991. **13**(5): p. 1018-22.
50. Dreyer, G., Addiss, D., Dreyer, P., & Noroes, J. , *Basic Lympoedema Management*, ed. H.P. Company2002, New Hampshire.
51. Das, L., G. Subramanyam Reddy, and S. Pani, *Some observations on the effect of Daflon (micronized purified flavonoid fraction of Rutaceae aurantiae) in bancroftian filarial lymphoedema.* Filaria J, 2003. **2**(1): p. 5.
52. Mukhopadhyay, A.K., *Lymphatic filariasis in Andhra Pradesh Paper Mill Colony, Rajahmundry, India after nine rounds of MDA programme.* J Vector Borne Dis, 2010. **47**(1): p. 55-7.
53. Krishna Kumari, A., et al., *Physical and psychosocial burden due to lymphatic filariasis as perceived by patients and medical experts.* Trop Med Int Health, 2005. **10**(6): p. 567-73.
54. Kumari, A.K., et al., *Health Related Quality of Life, an appropriate indicator to assess the impact of morbidity management and disability prevention activities towards elimination of lymphatic filariasis.* Filaria J, 2007. **6**: p. 8.
55. Michael, E., D.A. Bundy, and B.T. Grenfell, *Re-assessing the global prevalence and distribution of lymphatic filariasis.* Parasitology, 1996. **112 (Pt 4)**: p. 409-28.

56. Addiss, D.G., et al., *Clinical, parasitologic, and immunologic observations of patients with hydrocele and elephantiasis in an area with endemic lymphatic filariasis.* J Infect Dis, 1995. **171**(3): p. 755-8.
57. Ahorlu, C.K., et al., *Consequences of hydrocele and the benefits of hydrocelectomy: a qualitative study in lymphatic filariasis endemic communities on the coast of Ghana.* Acta Trop, 2001. **80**(3): p. 215-21.
58. Guyatt, G.H., et al., *What is "quality of evidence" and why is it important to clinicians?* BMJ, 2008. **336**(7651): p. 995-998.
59. Guyatt, G.H., et al., *Going from evidence to recommendations.* BMJ, 2008. **336**(7652): p. 1049-1051.
60. Kenney, M. and R. Hewitt, *Treatment of bancroftian filariasis with hetrazan in British Guiana.* Am J Trop Med Hyg, 1949. **29**(1): p. 89-114.
61. Pani, S., *DEC and supportive measures for the treatment of Brugian filariasis.* Nat Med J India, 1989.
62. Meyrowitsch, D.W., P.E. Simonsen, and W.H. Makunde, *Mass DEC chemotherapy for control of bancroftian filariasis: comparative efficacy of four strategies two years after start of treatment.* Trans R Soc Trop Med Hyg, 1996. **90**(4): p. 423-8.
63. Dunyo, S.K., F.K. Nkrumah, and P.E. Simonsen, *Single-dose treatment of Wuchereria bancrofti infections with ivermectin and albendazole alone or in combination: evaluation of the potential for control at 12 months after treatment.* Trans R Soc Trop Med Hyg, 2000. **94**(4): p. 437-43.
64. Yuvaraj, J., et al., *Impact of seven rounds of mass administration of diethylcarbamazine and ivermectin on prevalence of chronic lymphatic filariasis in south India.* Trop Med Int Health, 2008. **13**(5): p. 737-42.
65. Bernhard, P., P. Magnussen, and M.M. Lemnge, *A randomized, double-blind, placebo-controlled study with diethylcarbamazine for the treatment of hydrocoele in an area of Tanzania endemic for lymphatic filariasis.* Trans R Soc Trop Med Hyg, 2001. **95**(5): p. 534-6.
66. Hussein, O., et al., *Duplex Doppler sonographic assessment of the effects of diethylcarbamazine and albendazole therapy on adult filarial worms and adjacent host tissues in Bancroftian filariasis.* Am J Trop Med Hyg, 2004. **71**(4): p. 471-7.
67. Mackenzie, C.D., et al., *Lymphatic filariasis: patients and the global elimination programme.* Ann Trop Med Parasitol, 2009. **103 Suppl 1**: p. S41-51.
68. Fan, P.C., H.W. Peng, and C.C. Chen, *Follow-up investigations on clinical manifestations after filariasis eradication by diethylcarbamazine medicated common salt on Kinmen (Quemoy) Islands, Republic of China.* J Trop Med Hyg, 1995. **98**(6): p. 461-4.
69. Moore, T.A., et al., *Diethylcarbamazine-induced reversal of early lymphatic dysfunction in a patient with bancroftian filariasis: assessment with use of lymphoscintigraphy.* Clin Infect Dis, 1996. **23**(5): p. 1007-11.
70. Simonsen, P.E., et al., *Selective diethylcarbamazine chemotherapy for control of Bancroftian filariasis in two communities of Tanzania: compared efficacy of a standard dose treatment and two semi-annual single dose treatments.* Am J Trop Med Hyg, 1995. **53**(3): p. 267-72.
71. Meyrowitsch, D.W. and P.E. Simonsen, *Long-term effect of mass diethylcarbamazine chemotherapy on bancroftian filariasis, results at four years after start of treatment.* Trans R Soc Trop Med Hyg, 1998. **92**(1): p. 98-103.

72. Noroes, J., et al., *Pathogenesis of filarial hydrocele: risk associated with intrascrotal nodules caused by death of adult Wuchereria bancrofti.* Trans R Soc Trop Med Hyg, 2003. **97**(5): p. 561-6.
73. Meyrowitsch, D.W., P.E. Simonsen, and S.M. Magesa, *Long-term effect of three different strategies for mass diethylcarbamazine administration in bancroftian filariasis: follow-up at 10 years after treatment.* Trans R Soc Trop Med Hyg, 2004. **98**(11): p. 627-34.
74. McPherson, T., et al., *Health workers' agreement in clinical description of filarial lymphedema.* Am J Trop Med Hyg, 2006. **74**(3): p. 500-4.
75. Rajagopalan, P.K., et al., *Evaluation of integrated vector control measures on filariasis transmission in Pondicherry.* Indian J Med Res, 1988. **87**: p. 434-9.
76. Gordon, S., et al., *Lymphatic filariasis: a method to identify subclinical lower limb change in PNG adolescents.* PLoS Negl Trop Dis, 2011. **5**(7): p. e1242.

Table 1. Summary of studies that assessed the effect of antifilarial drug treatment on ADL, lymphedema, and hydrocele

Study	Country	Follow Up	Drug	Dose	Drug Dosing Schedule	Drug Delivery	ADL Effect	Lymphedema Effect	Hydrocele Effect
Kenney 1949	Guyana	1-3 months	DEC	0.5 -2.0mg per kg	Three times daily for 26 to 37 days	Clinical trial	.	+	.
Hewitt 1950	Guyana	8-14 months	DEC	0.2-2.6 mg/kg body weight	3 times daily for 11-39 days	Clinical trial	+	+¶	+
Beye 1952	Society Islands (Tahiti & Maiao)	16 months	DEC	2 mgm/kg body weight	Three times a day for 7 days	MDA, selective €	--	--	--
Kessel 1957	Tahiti	1 year, AA – 4 years	DEC	6 mg/kg body weight	Once a month for 1 year – variety of schedules	Selective	+	.	.
March 1960	Tahiti	10 years	DEC	6 mg/kg of body weight	Monthly doses for 12 months	MDA ъ	+	+	+
Ciferri 1969	American Samoa	2 years	DEC	6 mg/kg of body weight	Once a day for 6 days followed by: 1) no treatment for 1 year; then repeated same dose once a day for another 6 days 2) no treatment for 6 months; then repeat the same dose once a day for 6 days 3) one monthly dose for 6 consecutive months	MDA	+	--	--
Pani 1989	India	>1 year	DEC	6 mg/kg body weight	Daily for 12 days, repeated every 3-4 months for persistent edema	Clinical trial †	.	+ ‡	.
Partono 1989	Indonesia	11 years	DEC	5 mg/kg body weight	Daily for 10 days once a year in 1977 and 1980. Selectively in 1978, 1979, 1981 and 1982	MDA, selective	+	+	.
Fan 1995	Kinmen Islands	16 – 19 years	DEC	.33%		Salt	.	--	--

Simonsen 1995	Tanzania	1 year	DEC	6 mg/kg body weight	Daily in 3 divided doses for 12 days	Selective, MDA	·	·	--‡
					Single dose every 6 months for 2 years				
Meyrowitsch 1996	Tanzania	2 years	DEC	50 - 100mg or 0.33%w/w	Once a month for 1 year, distributed for 1 year	Clinical trial	·	--	+
Moore 1996	Gabon	1 week – 7 months	DEC	6 mg/kg body weight	Daily in 3 divided doses for 21 days	Case report	·	+	·
Meyrowitsch 1998	Tanzania	4 years	DEC	6 mg/kg	Daily for 12 days	Selective, MDA	·	·	+
					Single dose every 6 months for 1 year				
				50 mg to age <15 100 mg to age ≥ 15	Monthly single dose for 1 year				
				Salt	1 year				
Dunyo 2000	Ghana	1 year	IV	150-200µg/kg bodyweight	Single dose	Clinical trial	·	--	--
			Alb	400 mg					
Bernhard 2001	Tanzania	1 year	DEC	300 mg	Daily in 3 divided doses for 12 days	Clinical trial	·	·	--
Bockarie 2002	Papua New Guinea	5 years	DEC	6 mg/kg body weight	Single annual dose	MDA	·	+	+
			DEC + IV	6 mg/kg body weight and 400 µg/kg	Single annual dose				
Das 2003	India	1 year	DEC	25 mg	Twice daily for 90 days	Clinical trial	·	--	·
Noroes 2003	Brazil	18 months	DEC	6 mg/kg	Single dose	MDA	·	·	--
Hussein 2004	Egypt	2 years	DEC +ALB	6 mg/kg and 400 mg	Single dose annually	Clinical trial	·	·	--
					Daily for 7 days				
Joseph 2004	India	1 year	DEC	50 mg	Daily for 1 year	Clinical trial Δ	+	·	·

Meyrowitsch 2004	Tanzania	10 years	DEC	6 mg/kg	Daily for 12 days	Selective, MDA	.	.	+
					Single dose every 6 months for 1 year				
				50 mg to age <15 100 mg to age ≥ 15	Monthly single dose for 1 year				
Kerketta 2005	India	1 year	DEC	6 mg/kg body weight	Daily for 12 days, repeated once every 3 months for 1 year	Clinical trial Δ	+	+	.
Yuvaraj 2008	India	7 years	DEC	6 mg/kg	Single dose	Clinical trial	.	--	+
			Ivermectin	400 µg/kg					
Mackenzie 2009	Tanzania	4 years	IV + Alb	150-200 ug/kg body weight and 400 mg		MDA	+	.	.
Tisch 2011	Papua New Guinea	4 years	DEC	6 mg/kg body weight	Single annual dose	Clinical trial			
			DEC + IV	6 mg/kg body weight and 400 µg/kg	Single annual dose		+	.	.

Adapted from Addiss & Brady 2005

. Not evaluated or extremely small numbers

+ Decrease in size, incidence or prevalence noted (not necessarily statistically significant)

-- No decrease noted (of if noted, inconsistent or not considered significant by authors)

¶ - Disease progression also observed

‡ Reduction seen only in patients with early stage disease

ƀ Also had a vector control program

€ Mosquito sanitation and DDT spraying

Δ Had a foot care or limb care component

Table 2 Study characteristics of eligible publications assessing the affect of DEC, albendazole or ivermectin on clinical filarial disease

Study	Study Type	Sample Size	Clinical Assessment	Follow up
Kenney 1949	Clinical Trial of DEC dose	121 Total, 21 Hydrocele and 49 Elephantiasis	Physical examination, swelling assessed visually	1-3 months
Hewitt 1950	Clinical Trial of DEC dose	121 Total, 39 Elephantiasis	Physical examination and patient history	8-14 months
Beye 1952	Cross-sectional observational study	1265 Total, 70 Lymphedema, LAD, or Hydrocele and 369 ADL events	Physical examination and patient history	16 months
Kessel 1957	Prospective Cohort	2153 Total		4 years
March, 1960	Cross-sectional survey	339 Total, 237 Elephantiasis, 1220 Lymphangitis and 332 Hydrocele	Physical examination	10 years
Ciferri 1969	Cross-sectional survey	1,008	Physical examination	2 years
Pani 1989	Clinical Trial on recent vs. persistent edema	103 Recent edema 132 Persistant edema	Water displacement (volumes given)	>1 year
Partono 1989	Prospective Cohort	202 Total, 35 Elephantiasis	Physical examination-3 grades	11 years
Fan 1995	Prospective Cohort	416 Clinical cases	Physical examination-Measurement of lower limbs-mid-thigh, knee, mid-calf, ankle	16 – 19 years
Simonsen 1995	Community randomized trial	8 Hydrocele	Physical examination	1 year
Meyrowitsch 1996	Randomized, controlled trial	824 Total, 17 Elephantiasis and 41 Hydrocele	Physical examination of genitals, legs, and arms-graded	2 years
Moore 1996	Case Study	1 Lymphedema	Clinical, blood work, MRI, and lymphoscintigraphy	1 week – 7 months

Meyrowitsch 1998	Cross-sectional survey following RTC	43 Hydrocele	Clinical survey with examination-graded	4 years
Dunyo 2000	Double-blind, placebo controlled field trial	1425 Total, 48 Lymphedema, 54 Hydrocele	Physical examination with grading scale (0-3 for lymphedema and 0-4 for hydrocele)	1 year
Bernhard 2001	Randomized, double-blind, placebo-controlled study	98 Chronic Hydrocele	Ultrasonographic measurements of scrotum	1 year
Bockarie 2002	Cluster-randomized open-label	2500 Total, 110 Hydrocele and 68 Lymphedema	Physical Examination	5 years
Das 2003	Clinical Trial of DEC w/ or w/o Daflon	26 Lymphedema	Leg volume via water displacement	1 year
Noroes 2003	Prospective Cohort	569	Physical Examination and Ultrasound of scrotum	18 months
Hussein 2004	Ultrasound reports from a previous randomized clinical-trial-DEC/ALB dosage	58 Hydrocele	Scrotum ultrasound examination	2 years
Joseph 2004	Double-blind, placebo-controlled, clinical study of self-care of the affected limb and one of five treatments	142	Grading of lymphedema and water displacement volume measurements and serology, culture for ADL	1 year
Meyrowitsch 2004	Cross-sectional survey following randomized-controlled trial	21 Hydrocele	Lymphedema and Hydrocele graded	10 years
Kerketta 2005	Clinical Trial	300	Limb circumference measurements of both normal and affected limbs at three fixed points on the limb ADL: history	1 year
Yuvaraj 2008	Community randomized trial with prospective cohort	15 villages population ranging from	Cross-sectional surveys and clinical examination	7 years
Mackenzie 2009	Prospective Cohort	71	Physical examination	4 years
Tisch 2011	Community randomized trial with prospective cohort for AFM for DEC along vs DEC+IVM	~3500	Active surveillance for AFM by self report; Physical exam	4 years

Table 3 Assignment of quality grading score to publications included in analysis

Study	Study Type	Sample Size	Case Definition	Follow up	**Overall Quality**
Kenney 1949	High	Moderate	Low	Low	Weak
Hewitt 1950	High	Moderate	Low	Low	Weak
Beye 1952	Low	High	Low	Moderate	Weak
Kessel 1957	Low	High	Low	Moderate	Weak
March, 1960	Low	High	Low	High	Moderate
Ciferri 1969	Low	High	Low	Moderate	Weak
Pani 1989	High	High	Moderate	Moderate	Moderate
Partono 1989	Low	Moderate	Moderate	High	Moderate
Fan 1995	Low	High	High	High	Strong
Simonsen 1995	High	Low	Low	Low	Weak
Meyrowitsch 1996	High	Moderate	Moderate	Moderate	Moderate
Moore 1996	Low	Low	High	Low	Weak
Meyrowitsch 1998	Low	Moderate	Moderate	Moderate	Moderate
Dunyo 2000	High	High	Moderate	Low	Moderate
Bockarie 2002	High	High	Moderate	High	Strong
Das 2003	High	Low	High	Low	Moderate
Bernhard 2001	High	High	High	Low	Strong
Noroes 2003	Low	High	High	High	Strong
Joseph 2004	High	High	High	Low	Strong
Hussein 2004	High	Low	High	High	Strong
Meyrowitsch 2004	Low	Low	Moderate	High	Weak
Kerketta 2005	High	High	High	Low	Strong
Yuvaraj 2008	High	High	Moderate	Moderate	Moderate
Mackenzie 2009	Low	High	Low	Moderate	Weak
Tisch 2011	High	High	Moderate	Moderate	Moderate

Table 4 Characteristics of clinical trials assessing ADL episodes, lymphedema and hydrocele included in analysis.

Study	Inclusion Criteria	Exclusion Criteria	Blinding	Random-ization	Control Present	Con-founders	Limitations	Results
Hewitt 1950	Not Defined	Not Defined	No	No	No	Unknown	Dose ranges used in patients varied	Prevalence of clinical improvement, recurrence
Pani 1989	Defined	Not Defined	No	No	No	Yes	Multiple other supportive measures used: treatment of ADLA with 5 days of ampicillin, anti-inflammatories, Lasix and bandaging B. malayi lymphedema only	% Regression
Simonsen 1995	Defined	Defined	No	Yes	Yes and No	Unknown	Sensitivity of the diagnostic tests was too low to detect all individuals with infection in the initial survey, so some individuals with low intensity infections were missed and most men w/ hydrocele were MF negative	Number with clinical improvement
Meyrowitsh1996	Defined	Defined	No*	Yes	Yes	Yes	Amount of DEC given and the intervals between DEC intakes differed considerably between the control group and the salt trial group	% improvement and # of new cases
Dunyo 2000	Defined	Defined	Yes	Yes	Yes	Unknown	Low numbers did not allow statistical analysis of the data for elephantiasis and hydrocele changes	# with reduction, disappearance, or increase
Bernhard 2001	Defined	Defined	Yes	Yes	Yes	Yes		Reduction or increase in scrotal size and fluid volume

Bockarie 2002	Defined	Defined	No	Yes	No	Unknown	Efficiency of transmission varies among mosquito species, so conclusions may not be applicable to non-anopheline mosquitoes	Pre and post trial prevalence and % reduction, odds of lymphedema of the legs and hydrocele
Das 2003	Defined	Well Defined	Yes	Yes		No	Water displacement method not defined	% reduction in volume
Hussein 2004	Defined	Defined	No	Yes	No	Unknown	Study limited to clinically normal subjects	Presense of motile filarial worms, location and visualization of worm nests, changes in scrotal tissues
Joseph 2004	Well Defined	Well Defined	Yes	Yes	Yes	Yes	A 'rebound' effect observed when penicillin prophylaxis was halted Non-adherence	Incidence of ADL attacks
Kerketta 2005	Defined	Defined	No	Yes	No	Yes	Cannot differentiate the effect of DEC alone from that of the supportive measures	% edema reduction and ADL frequency
Yuvaraj 2008	Defined	Not Defined	No	Yes	No	Yes	Treatment of mf carriers detected during mf surveys prior to MDA 2. Hydrocele patients undergoing surgery not recorded 3.54–75% of the target population were treated at each round of MDA	Prevalence reduction and relative change
Tisch, 2011	Defined	Defined	Unknown	Yes	No	Yes	Observations conducted prior to WHO rec. for MDA with annual DEC + ALB Acute filariasis morbidity events were self-reported Design did not allow distinction between bacterial and filarial etiologies of AFM	AFM incidence

Table 5 Characteristics of epidemiologic studies assessing the impact of antifilarial drugs on ADL episodes, lymphedema and hydrocele.

Study	Inclusion Criteria	Exclusion Criteria	Confounders	Limitations	Results
Beye 1952	All persons living in the ten experimental areas age 0-50 years	None	Climate of areas, size of experimental areas, mosquito density of area, human population density of area		Prevalence of clinical filariasis (lymphangitis) and acute attack rate.
Kessel 1957		The elderly, those with chronic disease, and pregnant women	Vector control program	variety of dose schedules, efficiency of administration, new immigrants and visitors into a district, certain number of medication refusals	Lymphangitis attacks/yr and new cases of elephantiasis
March, 1960	Males living in seven widely distributed areas throughout the island.	All lymph node enlargement and lymphangitis evidently caused by current bacterial infection. Females.	Mosquito control by elimination of mosquito breeading places within 100 meters of each dwelling	Cross-sectional survey; no effort made to include the same persons in the second survey	Prevalence of lymphangitis and hydrocele, and those free from clinical filariasis
Ciferri 1969	All persons over 1 year of age living in each of the four American Samoa villages.	Borderline or minor cases of elephantiasis or hydrocele were excluded in the final data set.	Three different schedules of DEC administration were followed	Self-report of past and present history of filarial symptoms with physical examination.	Prevalence of elephantiasis, hydrocele, acute lymphangitis or hx of attacks; percentage change post-treatment
Partono 1989			4 species of malaria	B. timori endemic only	Reduction in rate of elephantiasis and ADL, incidence of new cases
Fan 1995	MF carrier with clinical dz in 88 villages of five towns/districts on kinmen Islands	51% of 814 pre-control mf carriers participated-unknown reason	Unknown		Rates of disappearance, significant improvement, no change, aggravation, and new occurance for lymphangitis, elephantiasis of the leg, hydrocele
Moore 1996	selective treatment for new residents, those with MF before initial tx, and hx of ADL over the past year	N/A	N/A	Case study design of only one patient	Resolution: legs symmetrical, eosinophilia normalized, MRI without evidence of edema, and lymphoscintigraphy with normal flow

Meyrowitsch 1998	All consenting individuals of the three villages aged greater than or equal to 1 year	Individuals under one year of age. Only males who completed the treatment, and in whom surgery had not been performed	Unknown	Dislike of repeated clinical examinations and blood sampling, combined with limited migration and some deaths, resulted in decrease in compliance from survey to survey.	% with more advanced stage of hyrocele, regression or complete disappearance
Noroes 2003	Men from 2 outpatient clinic infected with W. bancrofti with living adult worms detectable by ultrasound in the intrascrotal lymphatic vessels, and scheduled for DEC treatment with	Hydrocele or intrascrotal nodules detected on initial exam; hx of antifilarial tx, surgery or medical problems of genitalia; received antifilarial drugs or developed nodules during 18-month f/u	Unknown	US technician user error, experience	# of nodules, prevalence of acute and spontaneous resolution or increase in hydrocele size, frequency of acute hydrocele. Stepwise multiple logistic regression analysis on paratesticular nodule location, the presence of multiple nodules, and treatment with DEC
Meyrowitsch2004	All consenting individuals of three villages $\geq$ 1 year	The fourth community using DEC-medicated salt was excluded because they had also been given mass treatment with ivermectin since the original treatment.	Improvements in sanitation, migration out of the communities	23% of those examined in 2001 were below 10 years of age and were therefore not present during the 1991 surveys Treatment only administered once, not a reflection of large-scale mass DEC administration-based control programs	The prevalence of hydrocele and lymphoedema
Mackenzie 2009	LF cases from the Mafia district of Tanzania	Unknown	Unknown		Prevalence of cases who showed improvement,frequency of acute attacks,intensity of acute attacks, and lymphedema. # of new cases.

Table 6 Clinical assessment characteristics of included studies assessing the impact of antifilarial drugs on clinical filarial disease

Study	Clinical Assessment	Schedule	Case Definition
Kenney 1949	Physical examination, swelling assessed visually	Monthly	Lymphangitis and lymphadenitis - severe, regularly occurring attacks of lymphangitis, abdominal involvement, filarial fever, and pronounced, permanent swellings of the extremities which had existed several months to 30 yrs Elephantiasis-slight swelling of arms and legs of several months duration to massive, indurated, swellings involving the feet, legs, and thighs of many years duration
Hewitt 1950	Physical examination and patient history	Monthly	Symptomatic cases with history of a single attack of lymphangitis and lymphadenitis to severe, regularly occurring attacks of lymphangitis, abdominal involvement, filarial fever, and permanent swellings of the extremities from several months to 30 years
Beye 1952	Physical examination and patient history	Physical exam at baseline, 6 mo and 1 year and lymphangitis attacks recorded monthly	Clinical filariasis-hx of lymphangitis with at least: -Elephantiasis -Palpable epitrochlear lymph nodes in person > 10 yrs old -Varicocele, hydrocele, or greatly enlarged femoral nodes
Kessel 1957	Physical examination and patient history	Before, annually, and after treatment	Clinical filariasis- -Hx of lymphangitis -Enlarged epitrochlear glands -Hydrocele -Elephantiasis
March, 1960	Physical examinations	Before and after treatment	Enlarged nodes, lymphangitis, hydrocele, and other signs exclusive of elephantiasis
Ciferri 1969	Physical examinations	Before and after treatment	Signs of lymphangitis, adenopathy, hydrocele, and elephantiasis of limbs, genitalia, and breasts
Pani 1989	Water displacement (volumes given)	Before and after seven rounds of MDA	RO (Recent edema) pitting edema reversible on elevation PO (Persistent edema): patients w/ pitting or nonpitting edema, not reversible with elevation (with or without associated skin changes)
Partono 1989	Physical examination-3 grades	Annually	Defined into 3 categories: -Asymptomatic -Acute o recurrent adenolymphangitis and fever and/or scarring from suppurating lymph nodes -Lympedema or elephantiasis

Fan 1995	Physical examination-Measurement of lower limbs at mid-thigh, knee, mid-calf, and ankle	May to December 1993	Location, number, size and tenderness of lymph nodes recorded; extremities examined for swelling and measured for differences in size and for thickening or discoloration of the skin, measurements of lower limbs at defined points
Simonsen 1995	Physical examination	Pretreatment clinical survey + 1 yr reexamination	Hydrocele: ≥ 6 cm with fluid accumulation Elephantiasis: loss of contour due to swelling of the affected part (includes both lymphedema and elephantiasis)
Meyrowitsch 1996	Physical examination of genitals, legs, and arms with grading	Pretreatment clinical survey + 1 yr reexamination	Hydrocele: swelling in the scrotum >6 cm with fluid accumulation Leg elephantiasis: loss of contour due to swelling of the affected part (including both lymphedema and elephantiasis)
Moore 1996	Clinical examination, blood work, MRI, and lymphoscintigraphy	Case report	Lymphedema: swollen leg, hypereosinophilic, antifilarial ab positive, MRI evidence of subcutaneous edema in thigh, radionuclide lymphoscintigraphy demonstrating enhanced lymphatic flow
Meyrowitsch 1998	Clinical survey with examination and grading	Pre-treatment, one year, and four years after treatment	Hydrocele: swelling in the scrotum ≥6 cm with fluid accumulation Leg elephantiasis: Loss of contour due to swelling of the affected part (including both lymphedema and elephantiasis); graded as defined in 1995 study
Dunyo 2000	Physical examination with grading scale (0-3 for lymphedema and 0-4 for hydrocele)	At baseline and 12-months follow-up	Limb Lymphedema 1-Loss of contour due to swelling of affected limb with pitting edema 2-Nonpitting lymphedema with thickened skin and loss of elasticity 3-Evident elephantiasis with or without skin folds and warty growths Hydrocele (longitudinal diameter) 1-Swelling of the spermatic cord 2-Hydrocele 6-10 cm 3-Hydrocele 11-15 cm 4-Hydrocele >15cm
Bernhard 2001	Ultrasonographic measurements of scrotum	3, 6, + 12 months	Hydrocele-fluid volume indices (WHO-1992)
Bockarie 2002	Physical Examination with staging	Annually	WHO scale (stages 0-4). Expert committee on Filariasis Technical report from 1974. Subjects at risk for advanced hydrocele (male subjects ≥ 16 years) and moderate-to-severe lymphedema of the legs (subjects ≥ 21 years) scored positive for disease
Das 2003	Leg volume via water displacement with grading	Every 15 days to day 90, then days 180, 270, 360	Lymphedema: Grade I/II minimum for 6 months

Noroes 2003	Physical Examination and ultrasound of scrotum	24, 48, 72 hr; 7, 14, 21 d; and monthly until 18 months post tx	Hydrocele detected at physicial exam and confirmed by ultrasound Acute Hydrocele: increase of fluid in the tunica vaginalis space with appearance immediately or within a few days of nodule formation Chronic Hydrocele: unresolved during 18 mo f/u period, or that required surgical repair before the end of period due to a progressive increase in volume
Hussein 2004	Scrotum and ultrasound examination	Before tx and 3,6,12,18 and 24 months post tx	Hydrocele: presence of fluid ($\geq$ 2 mm thickness) surrounding the testis and epidydymis Subclinical Hydrocele: nonpalpable, but found on ultrasound
Joseph 2004	Lymphedema: water displacement volume measurements with grading ADL: serology and culture	Every 3 or 4 days during the 12 months of treatment and for the following 12 months	WHO 1992 Lymphedema grades: Grade I (pitting edema reversible on limb elevation), Grade II (irreversible edema with no skin changes) Grade III (irreversible edema associated with skin thickening) Grade IV (irreversible edema and severe skin changes) WHO 1991 ADL attack: local pain, warmth and tenderness, with either lymphangitis or lymphadenitis detected in the diseased or non-diseased limb ADL severity score: +1 for pain/tenderness, adenitis, angitis cellulitis, edema, fever, headache, malaise and GI symptoms; 0, 1 and 2 for <2, 2–5 and >5 days for duration of attack (max score = 11)
Meyrowitch 2004	Lymphedema and Hydrocele graded	Pre-treatment, one year, four, and ten years after treatment	Lymphedema and Hydrocele graded according to developmental stage
Kerketta 2005	Lymphdema: limb circumference measurements of both normal and affected limbs at three fixed points on the limb ADL: Patient history	Measurements taken on days 0, 90, 180 and 360. ADL history elicited by recall method every 14 days, ADL frequency at 1 year prior to tx and during 1 year of tx	Lymphedema graded according to standard criteria (WHO 1985): Grade 1 (pitting edema with mild fibrosis which is spontaneously reversible on elevation) Grade 2 (persistent edema, mostly non-pitting, with considerable fibrosis and not spontaneously reversible on elevation) Grade 3 (a profound increase in limb volume from lymphedema with marked dermatosclerosis with or without papillomata) ADL: episodes ascertained by the presence of local signs and symptoms such as pain, tenderness, local swelling and warmth in the groin or limb with associated constitutional symptoms such as fever, nausea and vomiting (WHO)
Yuvaraj 2008	Cross-sectional surveys and clinical examination	Prior to the first round of MDA and after the seventh round of MDA	Hydroceles were defined as unilateral or bilateral scrotal swellings, positive with both transillumination test and fluctuation test; they were not graded by size. Lymphedema was defined as unilateral or bilateral swelling of the limbs, with or without history of adenolymphangitis (ADL) attacks and graded into three categories (recent lymphedema, persistent lymphedema and elephantiasis) considering its duration, pitting and reversibility and skin condition (WHO 1992).

Mackenzie 2009	Physical examination at 1,2,4 and 10 years after start of treatment	once or twice each year	Acute attack signs and symptoms before MDA: feelings of fever, chills/shivering, deep pain in muscles, increased swelling, intense pruritic skin reaction, redness/warmth of skin, peeling of skin, swollen draining lymph nodes, nausea/vomiting
Tisch 2011	Active surveillance for AFM by self-report; Physical exam	Weekly; Annually	Painful swelling of the extremities, scrotum, and breast w/ the presence of fever during the previous week; Lymphedema and hydrocele defined by WHO