Systematic Review

Alternative mass drug administration regimens for Lymphatic Filariasis

· Report of findings ·

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Abbreviations

AE	Adverse Events
A	Albendazole
Ag	Antigen, referring to circulating filarial antigen
ALB	Albendazole
CDD	Community drug distributor
CFA	Circulating Filarial Antigen
D	Diethylcarbamazine citrate
DEC	Diethylcarbamazine citrate
EHCRN	Effective Health Care Research Nigeria
EU	evaluation unit
FTS	Filariasis Test Strip (Alere, Scarborough, ME, United States)
GAELF	Global Alliance to Eliminate Lymphatic Filariasis
GDG	Guidelines Development Group
GPELF	Global Programme to Eliminate Lymphatic Filariasis
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	Guidelines Review Committee
ICT	immunochromatographic test (BinaxNOW Filariasis ICT, Alere, United States)
IDA	ivermectin, diethylcarbamazine citrate, albendazole
IEC	Information, education and communication
IU	implementation unit
I	Ivermecting
IVER	Ivermectin
LF	lymphatic filariasis
MDA	Mass Drug Administration
MF	Microfilaria, microfilaremia
MMDP	morbidity management and disability prevention
MOH	Ministry of Health
NTD	neglected tropical disease
PC	preventive chemotherapy
PICO	Population, Intervention, Comparison, Outcomes
PV	Pharmacovigilance
RCT	Randomised Controlled Trial
ROB	Risk of Bias
RPRG	Regional Programme Review Group
SAE	Serious Adverse Events
SCIH	Swiss Centre for International Health
SD	Standard Deviation
STAG	Strategic and Technical Advisory Group
STH	soil-transmitted helminthiases
SURE	Supporting the Use of Research Evidence
Swiss TPH	Swiss Tropical and Public Health Institute
TAS	transmission-assessment survey
WHO	World Health Organization

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1 Background

The target date for global elimination of lymphatic filariasis as a public health problem is 2020. To date, 29 of 55 countries still requiring MDA are not 'on track' to reduce infection and stop treatment by 2020. Some countries are only now gaining momentum to scale-up MDA and realize that the current strategy requires a minimum of 5 years. Many governments and donors have committed resources only through 2020 and further commitments are not guaranteed. Countries just starting MDA implementation are now requesting advice from WHO on alternative strategies to help 'catch up' or provide a 'fast-track' for a chance of stopping MDA by the target elimination date. Additionally, some 'on track' countries are demanding guidance on how to deal with the following sub-optimal responses to current MDA strategies: -districts where the proportion of residents in sentinel and spot check sites remain >1% MF or >2% antigenaemia despite more than 5 annual MDA rounds (at least 1 country in all 5 regions; 5% of all districts)-districts with unsuccessful transmission assessment surveys (TAS) despite meeting eligibility criteria of 5 MDA rounds with effective coverage (at least 1 district in 12 countries, range of TAS failures by country ranges from 0-30% of all districts surveyed)-hot-spots of infection identified during post-MDA surveillance (Philippines, Sri Lanka, Indonesia, India)Countries expect WHO to recommend strategies to overcome these challenges. WHO must quickly respond to national programme queries by grading available evidence and establishing recommendations taking into consideration accessibility and feasibility of any alternative strategy [From WHO Guidelines proposal[1].

Alternative MDA strategies to the 5 annual MDA rounds as described above exist. Twice-yearly MDA with Ivermectin (IVER) has been referenced as one of the determinants of success in the elimination of onchocerciasis from the Americas and some foci in Africa [2,3,4,5]. Mathematical models agree that infection is reduced to below elimination thresholds in less time when twice-yearly treatment is delivered [6,7]. Historical pharmacokinetic (PK) studies are available for the current 2-drug MDA combinations. A ground-breaking PK study of a combination dose of all 3 currently recommended medicines (IVER, diethylcarbamazine citrate (DEC), Albendazole (ALB)) indicates superior parasite killing effects and no increased serious adverse events among persons with heavy parasite loads[8].

Use of alternative MDA strategies is assumed to stop transmission sooner and more effectively, while saving limited resources. The study by Thomsen et al prompted immediate expansion of 3 clinical trials. Data at 6 and 12 months is now available from 2 of 3 trials with similar findings and manuscripts are in preparation. The observed parasite killing effects suggest a possible permanent sterilization or destruction of adult worms. If confirmed, infection and transmission in endemic communities could be reduced below elimination thresholds in less time using this strategy than by using current strategies. Additionally, randomized clinical studies of this 3-drug strategy for community-wide treatment have been initiated in 5 countries and safety data was available for meta-analysis. Use of DEC in countries co-endemic with onchocerciasis and/or loiasis is not

recommended. Therefore, twice-yearly treatment with the current 2-drug regimen in these countries may serve as an alternative approach in such co-endemic settings.

To provide the WHO guideline development group with the best available evidence, the WHO requested the Swiss TPH to conduct an update of an existing systematic review (SR) on mass chemotherapy for lymphatic filariasis[9].

This report contains the methods and results of the **SR on effectiveness and safety** as well as the methods and results of the **feasibility scoping review of qualitative evidence on community perceptions** of mass drug administration regimens.

2 Methods

2.1 Systematic review on effectiveness and safety

We conducted a systematic literature review using standard methods[10] to answer the following question:

Which alternative strategies of mass drug administration are more effective than, and as safe as, the current strategy for LF elimination?

2.1.1 Criteria for selecting studies for this review

a. Types of studies

We considered comparative, individual and community studies with randomized allocation of drug interventions, in any language and publication status; including studies with individual- or community-level allocations of interventions. Cohort studies with cross-sectional measurement of prevalence before and after treatment with the interventions of interest were also included.

b. Types of participants

Individuals infected with or communities endemic for *Wuchereria bancrofti* or *Brugia spp*.

c. Types of interventions and comparisons

Based on the discussions with WHO, the following comparisons where considered relevant for the systematic review (see Table 1):

Table 1. Comparisons to be considered in this review.

Comparison	Intervention	Control	Context
1	IDA annual	DA annual	Onchocerciasis not co-endemic
2	IDA annual	IA annual	Onchocerciasis not co-endemic
3	DA biannual	DA annual	Onchocerciasis not co-endemic
4	IA biannual	IA annual	Onchocerciasis co-endemic
5	A biannual	A annual	Loiasis co-endemic

d. Types of outcome measures

Effectiveness outcomes:

- Microfilaria clearance
- Microfilarial density
- Circulating filarial antigen (as assessed by ICT/FTS[a])
- IgG4 response to BmR1[b] (Brugia Rapid or PanLF for *Brugia* spp.)
- Other markers of LF infection

Safety outcomes:

- Frequency of adverse events (AEs) of any grade or combination of grades
- Adverse events by participants sub-group and infection status

Adverse events were classified as follows:

- 0 No adverse event or within normal limits
- 1 Mild adverse event, does not interfere with work or school
- 2 Moderate adverse event, interferes with work or school at least 1 day
- 3 Severe and undesirable adverse event; interferes with activities of daily living (ADL), requires medical assessment
- 4 Potentially life-threatening or disabling adverse event; requires transfer to medical facility
- 5 Death

Serious adverse event - any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening. Grade 4 or 5 event was considered an SAE.

e. Data sources, search methods and eligibility of studies

We searched the following literature databases for the effectiveness and safety review:

[a] Where both ICT and FTS values were available, ICT these were used. ICT and FTS values were considered as being equivalent.

[b] This is not the indicator of choice for showing rapid decline post intervention. This is the indicator WHO recommends in transmission assessment surveys. However, we keep it here as requested by protocol reviewers.

- CENTRAL (The Cochrane Central Register of Controlled Trials)
- CAB Global Health (Ovid)
- Medline and in-Process Medline on the Ovid platform
- EMBASE
- Epistemonikos
- Scopus
- ClinicalTrials.gov
- WHO Global Health Library
- WHO International Clinical Trials Registry Platform (WHO ICTRP)
- Open Trials

The generic search strategy can be found in Annex 1.

We also searched for additional information from on-going trials from WHO and GDG members and checked for relevant studies in Tisch et al [9].

Individual-level safety-data from four on-going trials was supplied by the Washington University in St Louis [11].

Inclusion criteria:

- Published, unpublished and ongoing studies
- Primary data from five ongoing community studies (safety only)
- Comparative studies with randomized allocation of drug interventions
- Drugs to be considered in this review are:
    - Albendazole (ALB, 400 mg)
    - Diethylcarbamazine citrate (DEC, 6 mg/kg)
    - Ivermectin (IVER, 150-200 ug/kg)

Exclusion criteria:

- Regimens of any other medicine not listed under the inclusion criteria or comparisons of interest (see Table 1).

2.1.2 Study selection

References were imported into a reference management software and duplicates were removed. Unique titles and abstracts were screened for eligibility independently by two reviewers. Discrepancies in their assessment were solved by a third reviewer.

Full texts of included records were further assessed for eligibility by two reviewers. Companion records which could be linked to the same study were grouped.

Relevant studies were then independently, doubly scrutinised for inclusion by the reviewers team. Documents which were linked to the same study were considered as a single study.

2.1.3 Data collection

Data was independently entered by two different reviewers into a MS Excel template, containing a VBA form. Once comparisons of interest were defined, a third reviewer checked data item by data item with the original sources. Data was imported into R, where datasets were cleaned.

2.1.4 Risk of bias and quality of evidence

Risk of bias (ROB) of included studies was independently, doubly assessed by the reviewers team, using standard methods[10]. We present the ROB for each study and across studies. ROB criteria included:

- Sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blindness in the assessment of outcomes
- Blindness in data analyses
- Lost to follow up
- Incomplete reporting
- Funding sources
- Conflict of interests declaration

For observational studies, the same criteria were used, except for allocation concealment and blindness.

In the context of developing recommendations, we assessed the quality of evidence for all critical and important outcomes that potentially could influence decision making using the GRADE approach[12]. Grade includes the following criteria:

- Study design
- Risk of bias
- Inconsistency
- Indirectness
- Imprecision
- Other considerations: publication bias, confounding, effect size and effect gradient.

2.1.5 Analyses of effectiveness and safety outcomes

For binary outcomes, the effect estimates are expressed as the relative risk (RR) of the intervention compared to the control group, if they were reported as such or if data to calculate them were available. Otherwise, estimates as found in the documents are reported. For trials of the prevalence of infection in communities where before and after prevalence data were available, we estimated the additional change in prevalence in the intervention group compared to the control group, given the baseline differences. When the number of events was zero, we imputed a value of 1 to allow RR estimates to be calculated.

Microfilarial density is reported in geometric means and the effects were estimated as ratios of the geometric means (i.e. percentage change in the mean value of the intervention group compared with that of the control group). Where the density is reported to be zero, we arbitrarily imputed a value of 1 in order to allow the calculation. Where no standard deviation (SD), but ranges, were reported, SD was estimated assuming that ranges included 99% of data.

The proportion of participants with adverse events of different grades was estimated for the intervention and control arms. We used regression models with a log link and random effects for treatment effect by study and cluster and a fixed effect for study to estimate the relative risk of an adverse event in the intervention compared to the control arm.

Meta-analyses were carried out when more than one study reported on the same comparison, outcome and length of follow up. We assessed heterogeneity by estimating the I^2, the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), and using forest plots. We have consistently used random effects models in all pooled estimates. All estimates were reported with 95% confidence intervals.

2.2 Qualitative scoping review

The specific objectives of this qualitative scoping synthesis were to identify, appraise and synthesise qualitative studies exploring community and drug distributor (health workers and/or community drug distributors (CDDs)) perceptions and experiences of mass drug administration (MDA) campaigns for the elimination of lymphatic filariasis (LF) in countries undertaking disease elimination.

Population: Community and drug distributors

Community encompasses people receiving treatment as well as those around them. A drug distributor can be anyone distributing medicines from a doctor, community health worker or volunteer.

Phenomena of interest: Perceptions of and experiences with MDA campaigns for the elimination of LF, regardless of the specific treatment. We included any study that discussed community and/or drug distributor perceptions of and experiences with any form of MDA for LF elimination.

Context: Countries undertaking MDA campaigns for LF elimination

The synthesis focused on studies from countries undertaking MDA campaigns for LF elimination.

2.2.1 Inclusion criteria

We included all studies that utilised qualitative methods for data collection (e.g. focus group interviews, individual interviews, observation, document analysis) and qualitative methods for data analysis (e.g. thematic analysis, framework analysis, grounded theory). We excluded studies that collected data using qualitative methods but did not perform a qualitative analysis (e.g. open-ended survey questions where the responses are analysed using descriptive statistics). We included mixed methods studies where it was possible to extract findings derived from qualitative research.

However, for a number of these studies extracted data may have come from a combination of survey and qualitative data, as authors did not always distinguish the source of the findings specifically in the published article.

We included all studies with community members and drug distributors as study participants.

We included all studies that had a study focus on views and experiences of MDA campaigns for LF elimination.

2.2.2 Search methods for identification of studies

Electronic searches

We searched the following electronic databases for eligible studies from 2002 until February 1st 2017:

- Global Health Library
- WHO Global Health Library
- Embase (Ovid)
- MEDLINE (OvidSP)
- SCOPUS
- Web of Science

The search strategy was developed by an information specialist. Search strategies for each database using guidelines developed by the Cochrane Qualitative Research Methods Group for searching for qualitative evidence[13] as well as pulling keywords and mesh terms from a search for a qualitative evidence synthesis with a similar scope[14]. We chose these databases as we anticipated that they would provide the highest yield of results based on preliminary, exploratory searches. There was no date, language or geographic restrictions for the search. See Annex 2 for the complete search strategy.

Searching other resources

We conducted citation searches of included studies in Google Scholar, Scopus and Web of Science. We asked key people in the field to submit study titles that they thought would be relevant.

2.2.3 Data collection

Records identified from different sources were compiled into one endnote database and duplicates were removed. Titles and abstracts of the identified records were individually assessed by one member of the reviewer team to identify their relevance. Irrelevant references were discarded. Full text of all relevant papers were retrieved and reviewed for inclusion.

2.2.4 Data extraction and management

Data extraction was performed using a data extraction form designed specifically for this synthesis. The form was used to extract key themes and categories relevant to the synthesis objective. She also extracted information about first author, date of publication, language, country of study, context

(urban, rural), participant group (infected person, relative, community leader etc.), theoretical or conceptual framework, and research methods.

Data relevant to this systematic review, as defined in the preceding sections, was extracted using a predefine Excel template. Data items included:

- Geographical scope of the study
- Age and gender of participants
- Diagnosis technique used: volume of blood, test used (including commercial name)
    - Circulating filarial antigen;
    - IgG4 response to BmR1 (Brugia Rapid or PanLF for Brugia spp.)
- Other markers of LF infection such as disappearance of worm nests visible with ultrasound image techniques[a]: usg color Doplar.
- Detail of drug regimens
- Source / manufacturers of drugs used
- Outcomes (see above)
- AE definitions and classifications used
- Description of the AE active surveillance approach.

2.2.5 Appraisal of study quality

The inclusion criteria specify that to be included a study must have used qualitative methods for both data collection and data analysis. This criterion constitutes a basic quality threshold. HA discarded studies that did not meet this standard. In addition, to assess the methodological quality of included studies, HA applied a quality appraisal framework to each study. An adaptation of the Critical Appraisal Skills Programme (CASP) [15] quality assessment tool for qualitative studies was used. Other reviews of qualitative evidence have also used this tool [16,17,18]. The adapted tool that we used included the following eight questions:

1. Are the setting/s and context described adequately?
2. Is the sampling strategy described and is this appropriate?
3. Is the data collection strategy described and justified?
4. Is the data analysis described and is this appropriate?
5. Are the claims made/findings supported by sufficient evidence?
6. Is there evidence of reflexivity?
7. Does the study demonstrate sensitivity to ethical concerns?
8. Any other concerns?

We accept that there is no ‘gold standard’ approach for assessing the methodological quality of primary qualitative studies, but believe that this adapted CASP checklist best fits our needs.

[a] Important indicators to measure impact on adult worms.

2.2.6 Data Analysis

A thematic analysis was conducted using the Supporting the Use of Research Evidence (SURE) framework [19] to identify themes in the data. The World Health Organization (WHO) developed the SURE Framework to assist with evidence informed policymaking and technical capacity in low and middle-income countries. The framework has been used as an analysis framework in other studies and reviews [17, 20, 21, 22, 23, 24].

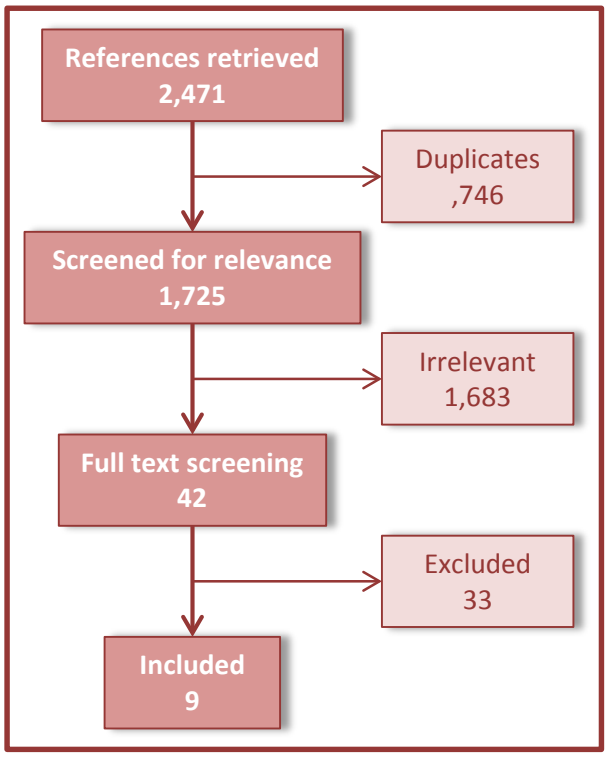
3 Findings I: effectiveness and safety systematic review

3.1 Overview of studies

3.1.1 Study flow

The literature databases searches yielded 2,458 hits. Additionally, we obtained 14 references from WHO partners, totalling 2,471 hits. After removing 746 duplicates, the remaining 1,725 records were screened for relevance by the reviewer team. 36 discrepancies in the relevance assessment between the two main reviewers were solved by an independent expert. From the 42 relevant articles 9 articles were included (see Figure 1).

Figure 1 Flow of studies – effectiveness systematic review.



Additionally, ongoing studies (e.g. DOLF, in several countries –Weil 2017) were identified by WHO and were added to the initial set of included studies. El Setouhi 2004 was finally excluded because comparisons-outcomes were judged as irrelevant. Annex 3 lists all evidence sources for this systematic review and Annex 4 contains the list of the 33 excluded studies and reasons for exclusion.

3.1.2 Characteristics of included studies

The studies were carried out between 2010 and 2017 (ongoing studies); all were reported in English and were located in African, Asian and LAC countries: Congo DR, Côte d'Ivoire, Haiti, India,

Indonesia, Liberia, Malawi, Mali and PNG. Each study involved areas in single countries except the ongoing DOLF study which applies the same protocol and Haiti, India, Indonesia and PNG.

Most of the studies were RCT, except DOLF-ongoing Indonesia (non-randomised, comparative study) and Pion 2017 (single arm study, but with data relevant to this review).

Age of participants in the studies was 18 years or older, except in DOLF-ongoing (although data from children under 5 years or participants weighting les that 15 Kg were excluded from the analyses), Kar 2017 and Pion 2017, which included 5 years old and older. The upper age limits of participants ranged from 55 to 80 years (18 years for Kar 2017). None of the studies considered gender in the selection or allocation of subjects, and only DOLF-ongoing showed gender disaggregated data.

The sample sizes of the individual trials ranged from 12 (six in each of the two study arms, Thomsen 2016) up to more than 10,000 (DOLF-ongoing), with a median of 102 individuals.

Allocation of trials to measure effectiveness was mostly at individual level, while safety studies allocation tended to be at community level.

See Annex 5 for the characteristics of included studies.

3.1.3 Assessment of risk of bias

Eight ROB criteria were assessed in all included studies. Sequence generation was ranked as low ROB in all studies which reported this feature (except in DOLF Libera) and it was unclear in six studies[a]. Concealment of allocation was characterised as unclear or high risk of bias across all studies, likely due to the fact that studies identified and sampled endemic communities and that interventions were at community level. Blindness in the assessment of outcomes and in the analyses of data were hardly reported; where reported they were categorised as low ROB in Dembele 2010, Kar 2015, Bjerum 2016 and in King 2017. Incomplete reporting was again unclear in many studies and only in Thomsen 2016 this was assessed as high ROB. Other criteria (i.e. reporting bias, disclosure of source of funding and conflicts of interest) were either not reported or classified as low ROB.

All criteria in Dembele 2010, Kar 2015, Kar 2017 and Bjerum 2016 were classified as low ROB (although some criteria were unclear); Thomsen 2016 had only one high ROB criteria and Tafatatha 2015 had three high ROB criteria. Most of the ROB criteria in the DOLF ongoing studies were unclear, due to reporting limitations.

[a] Each site in the DOLF ongoing studies are considered as an individual study.

3.2 Effectiveness and safety outcomes

In the next five sections (from 3.2.1 to 3.2.5) we report the findings of the systematic review following the five comparisons of interest shown in Table 1.

3.2.1 Ivermectin, DEC and Albendazole (IDA) compared to DEC with Albendazole (DA) where onchocerciasis is NOT co-endemic

For this comparison, effectiveness data was obtained from two studies (Thomsen 2015 and King 2017). Both reported MF clearance and microfilarial density suggesting effects favouring the interventions arms. The pooled estimate of the relative risk indicates that MF clearance in the intervention arm was significantly higher than in the control arm. The pooled ratio of geometric means of microfilarial density (mf/ml) between arms was 0.10 (0.07, 0.14), suggesting that in the intervention arm the geometric mean microfilarial density was 10 times lower than in the control group. This finding is consistent with the MF clearance data which showed a large proportion of subjects with MF clearance in the intervention arms, contributing to the total number of subjects with 'zero' microfilarial density in these arms (Table 2).

It is worth noting, though, that these data come from only two studies, one of which has a very small number of subjects in both arms (six in each, Thomsen 2016) and as a consequence carries less weight in the pooled estimate. Despite this, the direction and magnitude of the estimated effects and their confidence intervals provide strong evidence for an effect of the drug regimen.

King 2017 also reported on CFA (measured with FTS), where only one individual in each group became FTS negative after 24 months, producing a RR of 1 (CI 0.95 to 1.04).

Despite both studies being RCT, the overall GRADE quality of evidence for both outcomes was 'low', mainly due to the risk of bias of the underlying studies and imprecision of the estimate, particularly due to the small number of subjects in Thomsen 2016.

Table 2. Ivermectin, DEC and Albendazole (IDA) compared to DEC with Albendazole (DA) (onchocerciasis NOT co-endemic) – effectiveness data.

Study	Outcome	Intervention	Control	Effect (95% CI)			
Thomsen 2016	MF clearance	6 (N=6)	2 (N=6)	**2.60**	**0.94**	**7.17**	
King 2017	MF clearance	52 (N=54)	31 (N=55)	**1.71**	**1.35**	**2.17**	
- Pooled	MF clearance	58.0 (N=60)	33.0 (N=61)	**1.75**	**1.39**	**2.20**	I2 = 0% (p = 0.43)
Thomsen 2016	Microfilarial density (geom mean, mf/ml)	0.10 (N=6) SD:1.0	3.08 (N=6) SD:12.75	**0.15**	**0.06**	**0.40**	
King 2017	Microfilarial density (geom mean, mf/ml)	1.08 (N=58) SD:1.65	12.0 (N=58) SD:1.65	**0.09**	**0.06**	**0.13**	
- Pooled	Microfilarial density (geom mean, mf/ml)	1.18 (N=64) SD:1.0	15.08 (N=64) SD:12.75	**0.10**	**0.07**	**0.14**	I2 = 0% (p = 0.34)
King 2017	CFA prevalence	57 (N=58)	57 (N=58)	**1.00**	**0.95**	**1.04**	

Table 3 shows the analyses of non-published safety data from ongoing studies, kindly shared by Washington University in St Louis. These analyses include all participants older than 5 years and weighing at least 15 kilograms, of any infection status, taking into account the cluster design of the study.

The adjusted RR for any type of AE showed no difference in the pooled estimate (RR 1.10, CI 0.67 to 1.80). Only in India and Indonesia AE were more frequent in the intervention group (RR 1.31, CI 1.13 to 1.55 and RR 4.82, CI 1.67 to 13.88); effect that disappeared when data form the four countries was pooled together.

The estimates for grade 2 adverse events favoured the control group (e.g. there were relatively fewer adverse events in the intervention group compared to the control) except for Haiti. The pooled estimate suggested no evidence of a difference between intervention and control groups with wide confidence intervals.

The same pattern was observer for grade 3 and 4 adverse events, although the small number of subjects in all groups introduced substantial uncertainty into the individual trial and pooled estimates.

Analysis of grade 2 to 4 adverse events for the treatment naïve communities in Indonesia and PNG showed an advantage of the control condition in both communities (RR 1.28, CI 0.37 to 4.49; RR 1.55, CI 0.96 to 2.53 respectively). However, the pooled estimates suggested no evidence in the difference in the occurrence of grade 2 to 4 adverse events between the treatment arms in MDA naïve communities (RR 1.51, CI 0.96 to 2.39) or in MF+ individuals (RR 3.47, CI 0.68 to 17.73).

Serious adverse events (grade 4) only happened in three cases in Haiti. The absence of events made unfeasible and not really useful to estimate the adjusted effect across all four countries. However, crude estimates of SAE showed a RR of 0.48 (CI 0.08 to 2.90).

The GRADE quality of evidence was ‘low’ due to the risk of bias of the underlying study designs in which study areas were selected based on prevalence thresholds with random matching allocation of areas to intervention and control.

Further analyses by sub-groups and infection status can be found in Annex 6.

Table 3. Ivermectin, DEC and Albendazole (IDA) compared to DEC with Albendazole (DA) (onchocerciasis NOT co-endemic) – safety data.

Study	Outcome	Intervention	Control	Effect (95% CI)		
Unpublished - Haiti	Any AE	321 (N=3005)	429 (N=2991)	**0.67**	**0.51**	**0.89**
Unpublished - India	Any AE	339 (N=4051)	263 (N=4158)	**1.32**	**1.13**	**1.55**
Unpublished - Indonesia	Any AE	140 (N=2136)	114 (N=1785)	**4.82**	**1.67**	**13.88**
Unpublished - PNG	Any AE	299 (N=1294)	260 (N=1395)	**1.15**	**0.82**	**1.65**
Pooled	Grade2 AE	1099 (N=10486)	1128 (N=10329)	**1.10**	**0.67**	**1.80**
Unpublished - Haiti	Grade 2 AE	17 (N=3005)	43 (N=2991)	**0.42**	**0.24**	**0.72**
Unpublished - India	Grade 2 AE	34 (N=4051)	6 (N=4158)	**4.44**	**0.61**	**32.38**
Unpublished - Indonesia	Grade 2 AE	9 (N=2136)	6 (N=1785)	**1.67**	**0.78**	**3.55**
Unpublished - PNG	Grade 2 AE	39 (N=1294)	27 (N=1395)	**1.50**	**0.93**	**2.43**
Pooled	Grade2 AE	99 (N=10486)	82 (N=3005)	**1.27**	**0.26**	**6.19**
Unpublished - Haiti	Grades 3 and 4 AE	4 (N=3005)	12 (N=2991)	**0.42**	**0.15**	**1.18**
Unpublished - India	Grades 3 and 4 AE	1 (N=4051)	0 (N=4158)	**1.54**	**0.26**	**9.21**
Unpublished - Indonesia	Grades 3 and 4 AE	2 (N=2136)	0 (N=1785)	**36.03**	**7.46**	**174.09**
Unpublished - PNG	Grades 3 and 4 AE	0 (N=1294)	0 (N=1395)	**1.08**	**0.35**	**3.33**
Pooled	Grade 3 and 4 AE	7 (N=10486)	12 (N=10329)	**0.57**	**0.22**	**1.45**
Unpublished - Indonesia	Grades 2 to 4 AE MDA naïve communities	11 (N=2136)	6 (N=1785)	**1.28**	**0.37**	**4.49**
Unpublished - PNG	Grades 2 to 4 AE MDA naïve communities	39 (N=1294	27 (N=1395)	**1.55**	**0.96**	**2.53**
Pooled	Grades 2 to 4 AE MDA naïve communities	50 (N=3430)	33 (N=3180)	**1.51**	**0.96**	**2.39**
Unpublished - Haiti	Grades 2 to 4 AE MF+	2 (N=41)	5 (N=71)	**0.69**	**0.14**	**3.41**
Unpublished - India	Grades 2 to 4 AE MF+	18 (N=289)	0 (N=265)	**33.94**	**2.06**	**560.41**
Unpublished - Indonesia	Grades 2 to 4 AE MF+	2 (N=36)	0 (N=29)	**4.05**	**0.20**	**81.26**
Unpublished - PNG	Grades 2 to 4 AE MF+	7 (N=81)	6 (N=414)	**3.47**	**0.54**	**33.39**
Pooled	Grades 2 to 4 AE MF+	29 (N=447)	6 (N=414)	**3.47**	**0.68**	**17.73**
Unpublished - Haiti	SAE	0 (N=3005)	3 (N=2991)	**0.14**	**0.01**	**2.75**
Unpublished - India	SAE	0 (N=4051)	0 (N=4158)	**1.03**	**0.02**	**51.72**
Unpublished - Indonesia	SAE	0 (N=2136)	0 (N=1785)	**0.84**	**0.02**	**42.10**
Unpublished - PNG	SAE	0 (N=1294)	0 (N=1395)	**1.08**	**0.02**	**54.29**
Pooled (NOT ADJUSTED FOR CLUSTERING)	SAE	0 (N=10,486)	3 (N=10,329)	**0.48**	**0.08**	**2.90**

3.2.2 Albendazole with Ivermectin and DEC compared to Albendazole with Ivermectin for annual mass drug administration where onchocerciasis is NOT co-endemic

A single study addressed the second comparison of interest (Bjerum 2016 CIV), reporting on three outcomes: MF clearance, microfilarial density and adult worm nest clearance. The estimates for all three outcomes were in the direction of favouring the intervention arm with greater clearance and reduced microfilarial density, but was significant only in the case of microfilarial density (the confidence interval for microfilarial density excluding 1) (Table 4).

The overall GRADE quality of evidence was ‘very low’ for the three outcomes. The main reason was: high risk of bias of the study and considerations related to imprecision, as mentioned above.

Table 4. Albendazole with Ivermectin and DEC compared to Albendazole with Ivermectin (onchocerciasis NOT co-endemic) – effectiveness data.

Study	Outcome			Effect (95% CI)		
		Intervention	Control			
Bjerum 2016	MF clearance	29 (N=38)	11 (N=43)	**2.98**	**1.74**	**5.12**
Bjerum 2016	Microfilarial density (geom mean, mf/ml)	5.0 (N=38)	31.0 (N=43)	**0.16**	**0.12**	**0.22**
Bjerum 2016	CFA prevalence	35 (N=38)	43 (N=43)	**0.92**	**0.83**	**1.02**
Bjerum 2016	Worm nest clearance	17 (N=20)	7 (N=27)	**3.28**	**1.69**	**6.37**

Table 5. Albendazole with Ivermectin and DEC compared to Albendazole with Ivermectin (onchocerciasis NOT co-endemic) – safety data.

Study	Outcome			Effect (95% CI)		
		Intervention	Control			
Bjerum 2016	Serious AE (follow up: range 1 to 7 days)	0 (N=42)	0 (N=49)	**-**	-	-
Bjerum 2016	Grade 2 AE (follow up: range 1 to 7 days; subjective)	8 (N=42)	1 (N=49)	**9.33**	**1.22**	**71.61**
Bjerum 2016	Any AE (follow up: range 1 to 7 days)	16 (N=42)	19 (N=49)	**0.98**	**0.58**	**1.66**

3.2.3 Biannual DEC with albendazole (DA) compared to annual DA where onchocerciasis is NOT co-endemic

Two studies (Kar 2015 and Kar 2016) reported on MF clearance, microfilarial density and worm nest clearance at 24 months follow up (Table 6). MF clearance showed no evidence of a difference in both studies with point estimates close to 1 and confidence intervals containing 1, leading to a pooled estimate of 0.98 (CI 0.89 to 1.05). The estimates for microfilarial density suggest no evidence of an effect in the case of Kar 2015 and favouring the control group in Kar 2016. The pooled estimate of 1.23 (0.95, 1.59) indicates no evidence of an effect. Finally, the direction of the estimate for worm nest clearance favoured the intervention group, although with a CI which included 1.

Table 6. Albendazole with DEC; biannual compared to annual (onchocerciasis NOT co-endemic) – effectiveness outcomes at 24 months follow-up.

Study	Outcome	Intervention	Control	Effect (95% CI)			
Kar 2015	MF clearance	18.0 (N=26)	16.0 (N=25)	**1.08**	**0.73**	**1.60**	
Kar 2016	MF clearance	49.0 (N=51)	50.0 (N=51)	**0.98**	**0.92**	**1.05**	
- Pooled	MF clearance	67.0 (N=77)	66.0 (N=76)	**0.98**	**0.92**	**1.05**	I2 = 0% (p = 0.62)
Kar 2015	Microfilarial density (geom mean change, mf/ml)	5.0 (N=26)	9.0 (N=25)	**0.56**	**0.12**	**2.64**	
Kar 2016	Microfilarial density (geom mean change, mf/ml)	5.24 (N=49)	4.17 (N=51)	**1.26**	**1.13**	**1.40**	
- Pooled	Microfilarial density (geom mean change, mf/ml)	10.24 (N=75)	13.17 (N=75)	**1.23**	**0.95**	**1.59**	I2 = 5% (p = 0.31)
Kar 2015	Worm nest clearance	14 (N=15)	11 (N=13)	**1.10**	**0.84**	**1.44**	
Kar 2016	Worm nest clearance	4 (N=4)	3 (N=5)	**1.54**	**0.73**	**3.22**	
- Pooled	Worm nest clearance	18 (N=19)	14 (N=18)	**1.15**	**0.89**	**1.48**	I2 = 0% (p = 0.35)

The GRADE quality of evidence was 'low' due to the risk of bias of the trials (e.g. risk of bias in the selection of communities / participants and on allocation concealment) and to the imprecision criteria.

Another study, carried out in Indonesia, reported outcomes at 36 months follow up. This study actually reported before-and-after changes in the outcomes from three different geographical areas, two of them with annual DA ('control') and a third one with biannual DA ('intervention') (Table 7).

MF prevalence decreased in all three communities over time. However, in the intervention community the decrease was 1.69 (CI 0.53 to 5.37) times larger than in the other communities, although the CI of this effect was large, containing the no effect value of 1. The decrease in CFA prevalence over time was more pronounced in the intervention community as compared to the control communities (RR 2.33, CI 1.12 to 4.87) with a lower limit (1.12) close to but greater than 1. Finally, IgG4 response to BmR1 decreased in all communities with hardly any differences (RR 0.94).

Table 7. Albendazole with DEC; biannual compared to annual (onchocerciasis NOT co-endemic) – effectiveness outcomes at 36 months follow-up.

Study	Outcome	Effect (95% CI)		
DOLF-ongoing IND	MF prevalence - Pruda vs Paga & Levomada	**1.69**	**0.53**	**5.37**
DOLF-ongoing IND	CFA - Pruda vs Paga & Levomada	**2.33**	**1.12**	**4.87**
DOLF-ongoing IND	IgG4 response to BmR1 - Pruda vs Paga & Levomada	**0.94**	**0.61**	**1.44**

The GRADE quality of evidence is 'very low' mainly due to the fact that the study was observational, that there were remarkable differences at baseline and that there was serious imprecision in two of the outcomes.

3.2.4 Biannual Ivermectin with albendazole (IA) compared to annual IA where onchocerciasis is co-endemic

One RCT (Tafatatha 2015) and two observational studies (DOLF Liberia and DOLF MDA CIV) reported outcomes from this comparison. Tafatatha reported on MF prevalence suggesting hardly any effect with a RR of 0.87 and CI containing the no effect value of 1. The two DOLF studies compared changes in MF and CFA prevalence rates before and after the intervention. MF prevalence changes in intervention compared to control communities were inconsistent: the reduction in the intervention community was slightly higher than in control communities in Liberia, and favoured the control communities in Côte d'Ivoire. In both studies, the CI included the no effect value of 1; and in Liberia CI was extremely large (upper limit 20.14).

CFA changes were consistent in both studies, with estimates in the direction of reductions in the control compared to the intervention communities, but neither was significant and the pooled estimate suggested no evidence of an effect (RR 0.55, CI 0.17 to 1.82).

Table 8. Ivermectin + albendazole (IA); biannual compared with annual (onchocerciasis is co-endemic) - effectiveness outcomes.

Study	Outcome			Effect (95% CI)		
		Intervention	Control			
Tafatatha 2015	MF prevalence	13.0 (N=18)	15.0 (N=18)	**0.87**	**0.61**	**1.23**
		After	Before			
DOLF LIBERIA	MF prevalence - Middle 1 x MDA	0.0 (N=898)	1.60 (N=997)			
DOLF LIBERIA	MF prevalence - North 2 x MDA	0.0 (N=1133)	1.70 (N=1170)			
DOLF LIBERIA comparison	MF prevalence - MDA x 2	2.0 (N=2031)	36.0 (N=2167)	**1.26**	**0.08**	**20.14**
DOLF MDA CIV	MF prevalence - Abengourou 1 x MDA	3.30 (N=1635)	9.50 (N=1924)			
DOLF MDA CIV	MF prevalence - Akoupe 2 x MDA	3.60 (N=2009)	7.60 (N=1973)			
DOLF MDA CIV comparison	MF prevalence - MDA x 2	126 (N=3644)	133 (N=3897)	**0.83**	**0.53**	**1.28**
- Pooled	MF prevalence	128 (N=5675)	369 (N=6064)	**0.83**	**0.54**	**1.28**
DOLF LIBERIA	CFA - Middle 1 x MDA	1.80 (N=898)	12.50 (N=997)			
DOLF LIBERIA	CFA - North 2 x MDA	3.30 (N=1133)	13.60 (N=1170)			
DOLF LIBERIA comparison	CFA - MDA x 2	53 (N=2031)	284 (N=2167)	**0.55**	**0.31**	**0.97**
DOLF MDA CIV	CFA - Abengourou 1 x MDA	12.20 (N=1635)	24.20 (N=1924)			
DOLF MDA CIV	CFA - Akoupe 2 x MDA	14.80 (N=2009)	25.60 (N=1973)			
DOLF MDA CIV comparison	CFA - MDA x 2	496 (N=3644)	971 (N=3897)	**0.82**	**0.70**	**0.97**
- Pooled	CFA	549 (N=5675)	1255 (N=6064)	**0.55**	**0.17**	**1.82**

The GRADE quality of evidence in this comparison was 'very low' for all outcomes. This rating is due to the fact that the outcomes MF and CFA prevalence reduction were based on observational studies with high risk of bias, together with imprecision considerations.

Additionally, both observational studies DOLF Liberia and DOLF MDA CIV provided data on microfilarial density (Table 9). We estimated the relative change of this outcome before and after treatment. Microfilarial density largely decreased to zero after treatment in intervention and control communities in Liberia. In CIV, there was no evidence of a difference of schedule on microfilarial density (RR 1.36, CI 0.63 to 2.94 and RR 0.78, CI 0.35 to 1.71 for the two observed communities). [a].

Table 9. Ivermectin + albendazole (IA); biannual compared with annual (onchocerciasis is co-endemic) - effectiveness outcomes (additional data).

Study	Outcome			Effect (95% CI)		
		After	Before			
DOLF LIBERIA	Microfilarial density - Middle 1 x MDA	0.0 (N=898)	3.60 (N=997)	**0.14**	**0.01**	**2.55**
DOLF LIBERIA	Microfilarial density - North 2 x MDA	0.0 (N=1133)	2.80 (N=1170)	**0.16**	**0.01**	**3.06**
DOLF MDA CIV	Microfilarial density - Abengourou 1 x MDA	13.90 (N=1635)	12.0 (N=1924)	**1.36**	**0.63**	**2.94**
DOLF MDA CIV	Microfilarial density - Akoupe 2 x MDA	11.0 (N=2009)	13.90 (N=1973)	**0.78**	**0.35**	**1.71**

3.2.5 Biannual albendazole compared to annual Albendazole where loiasis is co-endemic

Finally, only one study addressed the biannual albendazole regimen in contexts where loiasis is co-endemic. This study (Pion) was a single arm, cohort study showing before and after differences at three years follow up (Table 10).

Table 10. Albendazole; biannual compared to annual (loiasis is co-endemic) - single arm study data.

Study	Outcome			Effect (95% CI)		
		After	Before			
Pion single arm	MF prevalence - 3 year(s)	2.0 (N=656) 0.30% 95%CI: 0.10 to 1.2	41.0 (N=772) 5.3% 95%CI:3.90 to 7.1	0.06	0.01	0.24
Pion single arm	CFA - 3 year(s)	31.0 (N=661) 4.7% 95%CI: 3.30 to 6.6	134.0 (N=773) 17.3% 95%CI:14.70 to 20.0	0.27	0.19	0.39

MF and CFA prevalence decreased after three years follow up at rates of 0.06 and 0.27 (94% and 73% reduction), respectively. These data were indirectly compared with the study of Ismail et

[a] Note that in order to be able to estimate changes in microfilarial density, which is expressed in geometric means, a value of 1 is imputed where density is zero.

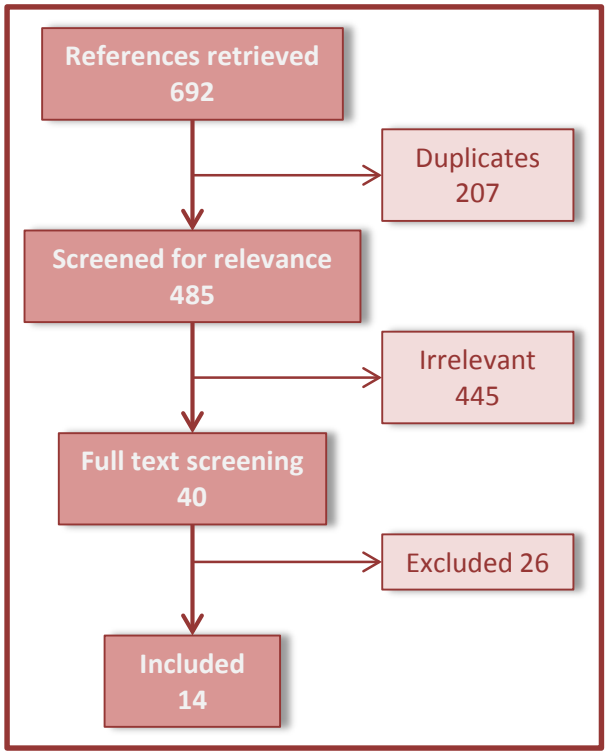
al.1998 although the follow up of the latter (15 months) was substantially different [25]. Only 1 of 15 subjects were MF clear and no patient cleared CFA at 15 months with 600 mg of Albendazole [25].

4 Findings II: feasibility scoping literature review

4.1 Characteristics of included studies

Our database search yielded 691 references. An additional reference was obtained by an expert, which lead to a total of 692 references. After removing 207 duplicates, 485 references were screened for relevance by one member of the reviewer team. 40 references were identified as relevant and full text was retrieved. For these references, the inclusion criteria were applied. Were appropriate, the study authors were contacted for further information. After excluding 26 references, 14 studies were included into the analysis (see Figure 2).

Figure 2. Flow of studies – feasibility scoping review.



4.1.1 Quality assessment of the included studies

HA did not use the quality assessment approach to exclude studies but rather to judge the relative contribution of each study to the development of explanations and relationships. All of the included studies had some methodological limitations associated with the way the qualitative portion of the study was conducted and/or reported. Five of the included studies had limitations that HA judged to be moderate to severe. It is possible that we can place less confidence in the findings from these studies than from those with only minor methodological issues (See Annex 8 table 14)

Fourteen studies were included in the synthesis. All of the studies were published between 2004 and 2016. Five of the included studies were mixed methods studies that employed some qualitative research methods and reported the qualitative and quantitative findings in the same article [SR01, SR03, SR05, SR07, SR08]. Two studies employed qualitative data collection methods and analysed the data qualitatively based on frequency of participants' responses [SR02, SR04]. Four studies reported the qualitative findings of the qualitative portion of a larger mixed methods study [SR09, SR11-SR13]. Only three of the included studies were purely qualitative research based on the descriptions within the studies themselves [SR06, SR10, SR14].

Health workers/CDDs were the sole participants in the qualitative methods in two studies [SR15, SR17]. Community members were the sole participants in the qualitative methods in two studies [SR11, SR14]. The remaining studies included both community participants and health workers/CDDs in the qualitative portion of the research.

All of the included studies were conducted in low and middle-income countries [SR15]: Philippines (N=1), Dominican Republic (N=1), Ghana (N=1), American Samoa (N=1), Papua New Guinea (N=1), Indonesia (N=1), Tanzania (N=2), Kenya (N=2), and India (N=4).

All of the included studies were published as papers in health research journals, which can lead to word limits that are not particularly well suited for reporting qualitative research. In general, there was poor reporting of context, sampling, research methods and researcher reflexivity across the studies. All studies gave some description, even if very brief, about the participants, sampling, methods and analysis. Most of the studies used interview or focus group discussions. The general lack of rich data and thick description in the studies may also have been due to the limitations set by journals publishing the studies.

In the following section, the findings and key messages of the synthesis will be presented using the headings and sub-headings from the SURE Framework. For a list of key messages, see table 2.

4.2 Key findings and messages of the synthesis

4.2.1 Community

a. Community members knowledge regarding LF and the MDA program

Six articles [SR11, SR12, SR09-SR11, SR14] discussed community members' knowledge of LF and the MDA program. In Tanzania, it was reported that neglected tropical diseases are not well known among policy makers, implementers and communities in endemic areas [SR09]. In both Tanzania and Papua New Guinea, most community members did not view LF as a current health problem affecting their communities.

"I think a long, long time ago, yes. But I do not see pom (swollen leg) nowadays". (Key informant interview)[SR14].

"Lymphatic filariasis is not a major problem in my area. There is nobody with elephantiasis. But those with hydrocele exist." (Religious leader, Morogoro Rural)[SR10].

Some participants in Indonesia [SR11] considered LF as a health problem that would detract from their economic earnings if contracted. Some urban participants in Tanzania also viewed LF as an ongoing health problem due to the presence of people with swollen legs.

In Tanzania[SR10], Elephantiasis and hydrocele were assigned different causes and there was confusion over the cause and mode of transmission of LF.

"There are mosquitoes of a particular species which bite people and cause elephantiasis. We don't know what causes hydrocele. Perhaps men themselves can be good experts in that because this happens in their environment." (Adult female, Lindi Urban) [SR10]

Amarillo 2008 [SR01] found that MDA programs led to an increase in knowledge and awareness of LF and helped to clarify community misconceptions. In contrast, Wynd 2007 [SR14] found that community misperceptions persisted even after MDA campaigns. For example, some community members believed that the tablets provided lifelong immunity.

"The benefit of the drug distribution is people are now in good health and they will never get sick with filariasis again in times to come". (Village FGD) [SR14]

Babu 2004 [SR02] found that most community members in India knew that LF could be eliminated. However, very few knew the benefits of MDA or that LF could be prevented by taking the medications. In Indonesia [SR11], some participants understood the benefit and importance of the MDA campaigns (i.e. that everyone needed to participate in order for the campaign to be successful). However, some chose to take natural medication instead of the tablets distributed during MDA campaigns.

In Tanzania, Kisoka 2016 [SR10] reported that the MDA program aimed to clarify that hydrocele and elephantiasis were both caused by LF. The program also tried to inform communities about the cause and mode of transmission. However, the above mentioned misperceptions persisted in the community revealing that the communication strategy being employed was not meeting its goals.

Key message:

Studies found that in general communities lacked knowledge about the cause and mode of transmission of LF and that hydrocele and elephantiasis had the same cause.

4.2.2 Community attitudes towards program acceptability

a. Positive perceptions of the MDA program

Four studies [SR03, SR10, SR11, SR14] found that when communities understood the benefits and aims of the program they were more open and accepting of MDA campaigns. They trusted that

MDA was beneficial to individuals and the community for disease prevention, cure and rehabilitation [SR10, SR11, SR14]. They understood that the goal of the program was disease elimination [SR10, SR11].

“Yes there are benefits; if a person is infected the drugs kill the infection and at the same time build immunity. If taken for five years the disease is eradicated completely. The mosquitoes that transmit the disease will no longer be able to do so; eventually there will be no more infections.” (Community leader, Lindi Rural) [SR10].

Three studies discussed community members’ beliefs in the positive effects of the drugs themselves [SR09-SR11, SR14]. Community members reported benefiting from the drugs directly when symptoms such as itching or attacks disappeared after MDA [SR09, SR10, SR14].

“The drugs are both preventive and curative. For people not yet infected when they take these drugs they don’t get the disease, for those with infections but no symptoms the parasites are killed. For those with early symptoms of the disease the symptoms disappear.” (Young female, Lindi Urban) [SR10]

Some believed that the tablets also cured other sicknesses.

“People are living in good health and this pill has cured some illness apart from pom”. (FGD Participant) [SR14]

Babu 2004 [SR03] found that people viewed the MDA campaigns more favourably when they were made aware of potential side effects before the drugs were distributed.

Three studies [SR08, SR11, SR14] found that communities were more accepting of MDA campaigns when community organizations, community leaders and churches were involved in drug distribution and seen to be publicly supporting disease elimination efforts.

One study, Njomo 2014 [SR13] reported that in Kenya, communities liked and accepted house-to-house drug distribution. This was because people could be reached in their own homes and they felt that the distributors would ensure that people who should not be taking the drugs did not receive them.

‘‘The system of house-to-house is the best because parents know their children’s age so it is easy to separate those who are not supposed to take drugs other than the system of putting the drugs in one public place where everybody comes and picks the drugs you will find that even those who are not eligible take the drugs.’’ (Female youth FGD in Shella sub-location)[SR13]

In Tanzania the community appreciated that the program was free of charge to participants [SR10].

Health workers in Tanzania [SR09] also perceived the community as becoming more positive and accepting of the MDA campaigns. Some noted that communities were taking the initiative to request drugs from health centres.

"… as time goes by, people have demonstrated interest in taking the drugs. For the first time, during this distribution, we have noticed people demanding drugs; they wait for distributors to visit them at their homes, while others come here to ask for drugs." (Health worker Lindi Rural) [SR09]

It was also noted that distributors were receiving a more open and welcome reception when arriving into communities [SR09].

Key message:

Studies found that when communities understood the benefits and aims of MDA campaigns for the elimination of LF and the potential side effects of the tablets they were more open to and accepting of the MDA campaigns.

b. Negative perceptions of the MDA program

Seven articles [SR02-SR04, SR09-SR12] presented findings related to negative community perceptions of MDA campaigns. Kisoka 2016 [SR10] found that the MDA campaign was not a priority for residents living in an area that lacked basic health care services. The community felt that the government should be focusing on more important aspects of health care than the elimination campaigns for LF [SR10].

"We don't want your drugs. Instead of bringing us important things you come with drugs." (Community member FGD) [SR10]

Four studies [SR02, SR03, SR10, SR11] found that the MDA program raised suspicions amongst community members for various reasons. These included:

- Questioning the program motives [SR03]
- Rumours that the drugs were meant to harm the population or caused serious side effects such as death [SR03, SR10, SR11]
- That the drugs were "not good" [SR02]
- That the circumstances surrounding the distribution of the drugs were suspicious [SR10]
- That the drugs were free [SR10]

"We don't trust free drugs; they have been brought to finish us off. People believe that these drugs have a hidden agenda that is the main reason; other reasons are just excuses. Free drugs are brought to kill us. People are afraid to use even the free bed nets provided. They don't use them to protect themselves or their children against mosquitoes but rather they use them to store their harvest." (Lindi Rural) [SR10]

The side effects caused by the drugs were another factor that influenced the negative views of community members [SR04, SR10, SR11]. In some cases, the negative perceptions came from the fact that community members could not see the passing of worms after they had taken the medication leading them to question why they were taking it [SR03].

The person selected to distribute the drugs could also influence community perceptions negatively [SR09, SR10, SR12]. In Tanzania, participants refused to take the drugs, as health workers did not distribute them. They felt that non-health workers distributing the drugs were not properly trained [SR09, SR10].

Njomo 2012 [SR12] found that participants in Kenya were willing to take drugs from community members as long as they knew them. Participants often refused to take the drugs from strangers.

“My village members in the last MDA questioned why strangers had to be brought to distribute drugs yet we have our own boys and girls who are well known to the villagers and have distributed these drugs previously, that is why people refused to take these drugs the last time compared to the first time when our own youth distributed the drugs and people really took the drugs.” (Female adult participant in one FGD in a low compliance village)[SR12]

Community members in Kenya felt that the practice of measuring height instead of weight for determining the dosage of ivermectin was problematic and lead them to refuse taking the tablets.

“This practice should be changed. It is better to measure weight for dosage because using height a child may take more tablets than the father and therefore cause misunderstanding.” (Young female, Lindi urban)[SR10]

Finally, if the timing of the drug distribution campaign was inconvenient to residents, for example during harvest or Ramadan, then they perceived the campaign negatively [SR09].

4.2.3 Motivation to participate in the MDA campaigns to eliminate LF

A number of articles discussed why people chose to participate or not participate in MDA campaigns. In the following section, I will present reasons participants expressed for taking and not taking medications distributed during elimination campaigns.

a. Reasons for participating in MDA Campaigns

Three articles [SR03, SR11, SR14] from Papua New Guinea, Indonesia and India briefly presented information about why communities participated in MDA campaigns to eliminate LF. The authors highlighted two factors. The first was the impact of community involvement. Babu and [SR03] found that when community groups and/or community leaders were involved in drug distribution more community members agreed to take the medication.

The second factor was whether LF and the MDA program were considered a priority. Both Babu 2004 [SR03] and Wynd 2007 [SR14] found that in communities where LF was considered a priority and the programme was considered beneficial had higher coverage rates.

“People are happy and willing to take the pills again because they do not want to get sick with filariasis”. (Respondent FGD) [SR14]

In Indonesia [SR11], other reasons mentioned for taking the tablets included:

- The tablets were from the government so they must be accepted

- Social pressure to conform especially when tablets were distributed in public areas
- Fear of others not complying
- Having become a community leader and wanting to set a good example
- To maintain a good social reputation

Trust in health workers

Two articles discussed the impact of the relationship between people taking the drugs and those distributing them on compliance. Amarillo 2008 [SR01], found that about a quarter of participants took the medication as they believed in the advice of the health worker. Health workers also played a large role in the dissemination of information about mass treatment.

Kisoka 2016 [SR09] discussed the strategy of selecting CDDs which aims to use the existing trust in a community to foster trust in the disease elimination program. In smaller communities, this seemed to work effectively with people commenting that they took the drugs as someone they knew distributed them. However, in larger or urban communities where not all households knew the distributor the same strategy did not work. Often a CDD would be known in some areas and a stranger in others. Some participants commented that they did not take the medication if a stranger and not the person they expected delivered it. Still others refused to take the drugs if they were distributed by a layperson instead of a health worker.

Key message:

Studies found that participation in MDA campaigns tended to be higher when; communities are involved in the planning and implementation of the campaign, the disease (LF) and MDA programs are considered a priority in the community, and those distributing the drugs, whether health workers or community drug distributors, are trusted in the community setting.

b. Reasons for not participating in MDA campaigns for the elimination of LF

The occurrence of side effects

Participants in six studies (SR01-SR04, SR11, SR14] made a direct link between the side effects they or others had experienced from the medications and the decision not to take the medications again.

Amarillo 2008 [SR01], found that the most common reason for not ingesting the tablets in the Philippino study site, besides forgetting, was the fear of side effects. These included drowsiness, headaches, abdominal pain and vomiting. Findings in Indonesia were similar [SR11]. Babu 2004 [SR02], also found that approximately one quarter of participants disliked the distributed drugs due to the side effects and that the “drugs were not good”. Wynd 2007 [SR14], found that only a small

number of young women in Papua New Guinea were not willing to take the medication due to side effects such as vomiting or dizziness as well as the excessive number of tablets.

Furthermore, Babu 2004 [SR03] and Babu 2010 [SR04], found that a fear of side effects in the Indian context lead to subsequent mop up activities being cancelled in many areas.

“Government is trying to prevent disease, but people are afraid to take these medicines. Something may happen after eating these medicines. So we are not willing to swallow.” (35 year old man, FGD participant) [SR03]

Babu 2010 [SR04] found that during a 2004 round of MDA up to half of the community members interviewed had not swallowed the drug due to a fear of side effects. They found that almost all of the participants had swallowed the tablets on the first day of distribution but that once adverse reactions appeared from the second day on they influenced the number of people willing to participate in the program.

In Indonesia [SR11] and the Philippines [SR01] community members decided to avoid taking the drugs due to the impact that the side effects would have on their income. Mostly day wage labourers felt that they could not risk losing a day’s work due to adverse reactions to the LF medication. In Indonesia [SR11], one participant sited potential economic loss from becoming ill with LF as the reason he took the tablets.

Amarillo 2008 [SR01] found that respondents had misconceptions about potential side effects which included sterility, fainting and death. Babu 2004 [SR03] and Babu 2010 [SR04], also found a fear of death as a reason for not taking the tablets in India. The reporting of deaths from the tablets raised suspicion amongst community members towards the MDA campaigns.

Other findings related to side effects were:

- Some male respondents refused to take the drugs as they would have to abstain from alcohol and cigarettes afterwards [SR01]
- Authors reported that a number of the adverse effects reported were actually representative of benefits of the medication, particularly the passage of worms [SR14]

Lack of information about LF, the campaign and the medications

Six studies [SR03, SR09-SR13] found that people did not take the medication due to a lack of information about the campaign itself or the medications included.

Babu 2004 [SR03] reported that in areas where LF was rare people did not know much about the disease and so gave very low priority to its prevention. This led to lower rates of coverage and compliance in certain areas of India. Kisoka 2016 [SR10] found that community members’ knowledge of LF in Tanzania was low, especially concerning the cause and mode of transmission. This led community members to believe that only infected people with visible symptoms needed to receive the medications. Some people refused to take the medications, as they felt they were not sick.

Babu 2004 [SR03] found that villagers in India did not know the date or time for when the medications were going to be distributed. Kisoka 2016 [SR09] had similar findings in Tanzania. Participants described being surprised and intimidated when drug distributors showed up at their houses as they had not received any information about the campaign and did not know it was happening. Njomo 2012 [SR12] reported that community members in Kenya were not satisfied with their communication and interaction with the CDDs. They believed that they had poor communication skills and had not given adequate information about the drugs.

“But the problem is that people were not educated on the drugs and the CDDs just came and gave out the drugs, they did not explain anything that is why many people did not swallow the drugs.” (Male youth FGD participant in a high compliance village)[SR12]

Two years later Njomo 2014 [SR13] reported similar findings. They found that lack of awareness and inadequate information about the MDA was the leading barrier reported by opinion leaders in their setting.

Kisoka 2016 [SR09] discovered that participants felt that they were lacking an explanation of the rationale and justification for taking the medications. This lead to not understanding the benefits of taking the medication and the campaign and in some cases a refusal to participate.

“Many people are refusing the drugs because they do not get information. They just hear from people who complain about the problems, so it becomes difficult to accept. Therefore, it will be better if people are first educated in order to accept the treatment, because they have the disease.” (FGD with adult men in Lindi Urban)[SR09]

“As it stands, there are no benefits of taking these drugs, but I can say if they explain to us about these drugs, then we can see the benefits. Otherwise, I don’t think there is any benefit.” (FGD with adult men in Lindi Urban)[SR09]

Rumours

A number of articles presented rumours linked to MDA that prevented people from participating in the program. Njomo 2012 [SR12] found that some community members in Kenya claimed that the drugs were not to treat LF but for sterilisation.

Kisoka 2016 [SR10] found similar reports in their exploration of community members’ perceptions of MDA in rural and urban Tanzania. They observed that there were fears in the population that the drugs were really being distributed to harm people, especially male sexual potency or to experiment on the population.

“Problems were that some people were refusing to accept the drugs due to the belief that drugs cause male impotence and when the father refuses, all people in that household also refuse.” (CDD, Morogoro Urban)

CDDs and community members thought that this could be one of the reasons for low drug uptake. The authors concluded that the lack of explanation for the adverse effects most likely fuelled the existing rumour about the drugs and the aim of their distribution [SR10].

Rumours about drug side effects were also reported in India and Indonesia, including reports of fatalities from the drugs distributed during the campaigns [SR02-16, SR11].

i. Other reasons mentioned for not participating

Three studies brought up further reasons for non-participation in MDA activities. These are listed below:

- Lack of trust [SR03]
- Loose tablets without labels arouse suspicion [SR03]
- An excessive number of pills [SR14]
- Forgetfulness [SR11, SR14]
- Too busy [SR11]
- Had heard that everyone else had complied so did not feel the need to take the tablets as the community was protected [SR11]
- Having to take time off work to go and swallow the tablets [SR11]
- Contraindications such as being pregnant or breastfeeding [SR11, SR14]
- That the drugs were chemically manufactured (not natural) and participants were unsure of what they would do to their bodies [SR11]
- Had tested negative for LF [SR11]

Key message:

Studies found that participation in MDA campaigns tend to decrease when; side effects are experienced or feared, when there is a lack of information about LF, the tablets or the campaign available to community members or when communities believe rumours about the tablets or campaigns that raise doubts and suspicion.

4.2.4 Providers of care: Health workers and drug distributors

a. Knowledge of LF and MDA programs

Five articles (13, SR02, SR07, SR09, SR10] discussed health worker and drug distributors' knowledge of LF and the MDA program. In Tanzania, it was reported that neglected tropical diseases are not well known among policy makers, implementers and communities in endemic areas [SR09]. In the Philippines [SR01], health workers considered LF to be a serious problem with those who are infected being unable to work, becoming physically deformed and stigmatised and not being able to find a partner or get married. In Tanzania [SR10], health workers acknowledged the presence of LF due to their involvement in the MDA program but did not raise it as an everyday

health issue. CDDs in Tanzania felt that elephantiasis was not a problem in their communities but hydrocele was. They had conflicting views as to the cause and transmission of the disease due to differences in the training they had attended. These misconceptions were often passed onto the community during MDA campaigns when CDDs were tasked with providing information to community members.

“From what I learned in school it is transmitted by mosquitoes, but we were not told so in this MDA.” (Morogoro Urban)[SR10]

“As far as I know hydrocele is that disease which a man can get as a result of filling up with liquid. We call it ngiri maji. Elephantiasis is a disease, which a person gets from worms that are found in the water. The person gets the disease by entering into the water and being bitten by insects living in the water with worms.” (CDD, Lindi urban)[SR10]

In India [SR02], health workers believed that mosquito control was the most important factor for controlling LF. Most knew of MDA and thought that LF could be eliminated. However, very few health workers knew the benefits of MDA or that the disease could be prevented using drugs [SR02]. Some considered elephantiasis synonymous with LF. They mentioned that since they were not observing many lymphedema cases in their areas that they were not at risk for getting the disease [SR07].

The only article to talk about drug preferences was Babu 2004 [SR02]. They reported that DEC was the drug of choice. However, health workers were uncertain about why it was being given to the whole community. Most had a negative perception of the quality and effectiveness of the drug and did not like the large amount of side effects experienced. Not all health workers knew that albendazole was also being given and that it had a deworming effect. They believed that communities should be better informed of the benefits of the MDA program and the side effects of the drugs. The same study [SR02], found that NGOs working with the MDA program were lacking knowledge about the rationale and benefits of the program.

Key message:

Studies found that often health workers had a good understanding that LF was a problem in their setting, of the cause and mode of transmission of LF and that hydrocele and elephantiasis had the same cause. However, this knowledge was not as prevalent amongst community drug distributors who often had misconceptions surrounding the topic.

b. Health worker and CDD attitudes towards program acceptability

Five articles [SR02, SR09, SR10, SR12, SR13] presented findings about the positive attitudes of health workers and drug distributors towards the MDA program. In India [SR02], medical officers viewed the program as useful for the local people and had a generally positive attitude towards it. In

the same study, NGOs involved in the program also viewed it positively and wanted to be involved in future MDA campaigns [SR02].

In Tanzania [SR10], drug distributors felt that the program had reduced the problems associated with LF in their communities. They perceived MDA activities positively and believed it was beneficial to both individuals and the community. Local health workers also felt that the campaign was important and walked along with distributors to ensure that they reached every house. These health workers believed strongly in the drugs and felt it was their duty to exert some pressure on people who refused to take them [SR09].

Four articles [SR02, SR09, SR10, SR12] also presented findings of negative attitudes of health workers and drug distributors towards the MDA program. Most of the negative perceptions were linked to the distribution process. Medical officers in India [SR02] were not happy with the method of distribution, especially that the drugs were distributed by non-medical personal. In Tanzania, distributors were negatively received in the community and sometimes insulted or belittled [SR09].

“If these drugs were meaningful [important], do you think they would allow you to distribute them?” (Elderly community member to a drug distributor)[SR09]

Health workers and drug distributors in Tanzania and Kenya had negative perceptions of the drug distribution [SR10, SR12]. These included negative reactions from community members, little or no trust in their abilities from community members, difficulties in reaching communities given the terrain and the short time allocated for distribution [SR10].

4.2.5 Health worker and CDD motivation to participate in the MDA program

Four articles (13, SR05, SR10, SR12] discussed factors that motivated health workers and CDDs to participate in MDA programs. In the Philippines [SR01], health workers were motivated to continue working with MDA due to the decrease in the number of positive cases of LF in their communities, the increase in people’s awareness and knowledge about the disease and the clarification of various misconceptions regarding antifilarial drugs.

In the Dominican Republic [SR05], staff were motivated by increased job satisfaction after being integrated into the larger public health program. This integration allowed them to participate in other programs such as vaccination and due to extra support complete the MDA tasks more quickly.

In Tanzania, some distributors were motivated to participate in the MDA program as they felt it improved their communication skills. They felt pride and growing self-confidence in their ability to communicate with different stakeholders. This improved communication gave them increased respect from community members as they were more clearly able to explain the rationale and benefits of the campaign [SR09].

In Kenya, CDDs were motivated to participate when they were recognized and received items such as t-shirts as tokens of appreciation [SR12].

Three articles [SR06, SR09, SR13] discussed factors that decreased motivation to participate in MDA campaigns. In Ghana, difficult physical access to communities during MDA campaigns and the lack of financial incentives decreased motivation to participate [SR06]. In Tanzania, lack of financial incentives also played a role along with the limited amount of time given to distribute the drugs and the negative reception in some communities [SR09]. Finally, in Kenya, distributors found it difficult when the awareness programs conducted before campaigns had not adequately informed the communities about the MDA campaign. They also felt that more distributors were needed to complete the MDA campaign and they wanted adequate training for their position.

4.2.6 Health systems factors

a. Financial resources

Three articles [SR06, SR09, SR12] mentioned findings related to the financial resources, beyond incentives for drug distributors (discussed later), provided to MDA programs. In Tanzania [SR09] and Ghana [SR06] researchers highlighted that the delayed release of funds from donor agencies affected the implementation calendar and lead to a delay in starting the campaign and the release of education and communication materials. This often led campaigns to be in conflict with important cultural events or other public health programming. In Tanzania [SR09], the late release of the drugs was also observed.

Studies in Tanzania [SR09], Ghana [SR06] and Kenya [SR12] reported financial resources issues linked to the amount of funding for drug distributors. This lack of funding lead to the following challenges:

- The MDA programs can be pushed aside in favour of programs with more money [SR06]
- Lack of funding makes it difficult to recruit distributors [SR06, SR12]
- Lack of funding leads to hiring of an insufficient number of distributors [SR12]
- The funding provided for distributors does not cover the amount of time they need to complete the distribution [SR09]
- Distributors were not compensated for the extra time needed to complete the distribution therefore some stopped distributing when the allocated time was over not reaching every household [SR09]
- Distributors used personal funds to cover costs associated with the MDA program [SR09]

b. Human resources

Nine studies (13, SR03-SR07, SR10, SR12, SR13] mentioned findings related to human resources use during MDA programs. The most frequently mentioned was the importance of the involvement and support of all levels of health care services in the MDA program (13, SR03, SR05, SR13]. In many instances studies reported that when this involvement and support existed compliance increased (13, SR03, SR05]. In other cases increased support from the higher levels of the health services and government were needed to increase the success of the program [SR01, SR05]. In India [SR03, SR04], health personnel not involved in the drug distribution were engaged to treat side effects. Where this happened side effects did not seem to negatively affect the program.

A number of articles [SR04, SR06, SR12] mentioned the supervision of drug distributors. The main finding was a lack of supervision of drug distributors during MDA campaigns [SR06, SR12] due to the already high workload of the supervisors [SR06]. Supervisors were sometimes left to finish the reporting and tallying that was incomplete, adding to their already large workload [SR06].

In Kenya [SR12, SR13], an insufficient number of drug distributors was reported. In India [SR07] and Tanzania [SR10] a lack of health workers in general was reported. Participants were frustrated over the poor health care offered in their areas.

Key message:

Studies found that the involvement of and support from all levels of healthcare services in the MDA campaigns was important for the success of the program.

Studies found that there was a lack of supervision of community drug distributors during MDA campaigns.

Studies found that in general there was an insufficient number of people involved in distributing tablets during MDA campaigns.

4.2.7 Recruitment and training of drug distributors

a. Recruitment and selection

Three studies [SR09, SR12, SR13] discussed the recruitment and selection of drug distributors. In Kenya, CDDs were selected during Chief's meetings where the communities were also informed about the upcoming MDA campaign [SR13]. However, a number of CDDs believed that the process of selection was not transparent [SR12]. CDDs in this area were selected based on education, having volunteered in past community programs, good behaviour and familiarity with village members. Some felt obligated to accept as many people disliked volunteer work and would not participate [SR12].

In Tanzania [SR09], the selection of CDDs was not as clear. In some settings, the community chose them. However, in other settings, influential people such as community leaders or health workers, appointed them contrary to the aim of the MDA program. Selection criteria ranged from previous experience to a willingness to participate. The selection of CDDs often caused conflict in community settings. In one instance, health workers had overruled the community leaders pick for CDD believing that an appropriate selection process had not been followed. Consequently, the community leaders worked to convince their community to refuse the drugs and pulled their support for the program.

b. Training

Many articles [SR03, SR06, SR07, SR09, SR10, SR12, SR13] reported findings related to the training of CDDs. Inadequate training, or in some cases no training at all, was reported as a finding in a number of studies [SR07, SR09, SR10, SR12, SR13]. The following problems were highlighted:

- Short training session occurring too close to the distribution day did not allow for the distribution of information and messaging to the community before the start of the campaign:

  "The message for the purpose of MDA in the village is not reach the people properly. This is the main cause of non-consumption. The training should be given way before the program commences. We did the training quickly, so we could not do the program justice." (Medical officer) [SR07]
- Reported training times of 1-3 hours over three days were inadequate to prepare distributors with the knowledge of the disease and distribution needed to complete their task [SR09]
- Inadequate training lead to misinformation being passed on to the community about the MDA program, the cause of LF, how it is transmitted and the benefits of taking the drugs [SR09, SR10]
- When training of CDDs was perceived as inadequate by community members they were more likely to refuse to take the tablets [SR10]
- CDDs identified their training as inadequate and believed better training would have benefits to the MDA program [SR13]

Babu 2004 [SR03] found that when training was conducted as planned and covered communication skills, the disease and its prevention, compliance rates were high.

Two studies [SR09, SR12] mentioned who conducted the training. In Tanzania, the training was conducted by health workers or ward health officers (lay people employed by the government to oversee preventative activities at community level) [SR09]. In Kenya, training was conducted by health personnel [SR12].

Four studies [SR06, SR09, SR12, SR13] mentioned findings related to the content of the training received by CDDs.

In Ghana [SR06], a participant discussed the various components of the training he received:

"Yes we were trained before we started to distribute the drugs. Our supervisors made us to understand that when we go, we have to write the name of the household head and then we use the stick I talked about to measure the height of the rest of the household. According to the measurement, if you deserve to be given four (tablets of ivermectin), we give you and then add one of the big ones (albendazole tablet)." (CHV, FGD, Ahanta West)[SR06]

In addition to the components described in the quote above, CDDs received training in communication skills [SR03], the disease and its prevention [SR03], the rationale for treatment [SR09] and the need to observe the drug being swallowed [SR13]. One article stated that the content of the training was consistent with WHO's recommendations [SR12].

Key message:

Studies found that in general community drug distributors did not receive adequate training to fulfil their duties during MDA campaigns.

4.2.8 Incentives

Five studies [SR05, SR06, SR09, SR12, SR13] set in the Dominican Republic, Ghana, Tanzania and Kenya, mention incentives for drug distributors. These can be classified into monetary incentives, support and items (such as T-shirts and badges). Incentives were perceived as positive when participants felt that the remuneration they received was adequate and demonstrated an appreciation of their time and effort. However, when remuneration was perceived as being too little it influenced the motivation of the distributors and could lead them to drop out of the program. Incentives could also influence who was selected to become a CDD. In Tanzania [SR09], some health workers feared that community leaders were appointing their relatives because of the incentives. In this case, the health workers feared that it would negatively affect the distribution and appointed community health workers instead. This caused some of the community leaders to not participate in the program.

a. Monetary incentives

In some settings, monetary incentives did not seem to play a large role in CDD motivation or satisfaction whereas in other settings a perceived lack of monetary compensation led some CDDs to drop out of the program.

In the Dominican Republic, the monetary incentive was a per-diem to cover the cost of lunch. Both the community volunteers and the primary health workers were given the same amount as they were working together. In Kenya [SR12, SR13], CDDs received monetary allowances for training attendance and transportation. Lunch was also raised as something that CDDs should receive while they were distributing medication.

In Ghana [SR06], lack of monetary incentives was linked to decreased motivation among CDDs. Here CDDs reluctantly volunteered for the LF program as the remuneration they received was less than from other public health programs in the area and the work is very gruelling. The low payment was also a reason for some to opt out of the program and follow other financial opportunities with other programs or work. This lead to less people available to distribute the drugs making reaching targets more difficult within the allotted time and causing delays in reporting. CDDs linked an increase in remuneration with an increase in motivation and love for the work.

“The money has to come. The volunteers have to get something to motivate them. If funds are raised for them, it’ll increase their ‘taste’ for the job. And we to, (supervisors) you should help us too, we will do our best to spread the message more so we can do the one-on-one and door-to-door.” (Sub-district Supervisor, IDI, Nzema East)

b. Support

Only one study in Kenya [SR12], mentioned support as an incentive that CDDs considered important. A few CDDS received moral support through recognition and invitation to community health programmes.

c. Items

In Kenya [SR12, SR13], T-shirts and badges were an important incentive from the CDDs' point of view. T-shirts and badges allowed the distributors to be recognizable within their settings. This was important to CDDs giving them outward recognition of their role within the campaigns. T-shirts, kept after the campaign was over, were also seen as a token of appreciation for the work they had done.

A CDD in Ghana believed if they were given bicycles, it would facilitate their work, especially concerning reporting and delivery of items back to the health station.

"I believe if we're given bicycles, it'll be helpful. That way if our supervisor is unable to come for the books on time, we can bring them to the health centre ourselves." (CHV, FGD, Nzema East)

Key message:

Studies found that incentives were important for drug distributor motivation when they were perceived as adequate and a demonstration of the appreciation of their time and effort. However, if the remuneration was perceived as not enough or less than what was offered in other public health programs it influenced distributor motivation and could lead to leaving the program.

4.2.9 Accessibility of care

a. General

Two studies set in Tanzania [SR09, SR10] discussed participants' general frustration with the lack of health care services in their communities. In some cases, when general health care and services were poor and or lacking, it lead to a decreased trust in health workers and communities to believe that the MDA campaigns were not a good use of resources.

Amarillo 2008 [SR01] specifically raised the issue of a lack of information, education and communication materials available at local health centres in local languages in the Philippines. The available materials focused on LF and did not discuss MDA.

b. Accessibility to treatment for side effects

Three articles [SR03, SR04, SR12] raised findings related to the accessibility to treatment for side effects after the tablet ingestion. In India it was reported that local primary health centres managed side effects [SR03], CDDs were able to distribute medication for side effects [SR04], and doctors

from mobile health units were on hand to help deal with adverse reactions [SR04]. Some community members did not seek treatment for side effects [SR04]. In this setting, side effects were not perceived to be a big problem for the MDA program by health workers. However, in contrast, community members believed that they were a large problem and one of the main reasons for not taking the tablets [SR04]. In areas where side effects were treated by health personnel compliance seemed to be higher [SR03]. In Kenya a number of community members highlighted the importance of side effect control to increase compliance levels [SR12].

Key message:

Studies found that access to and the provision of treatment for side effects during MDA campaigns could help to increase coverage and compliance.

4.2.10 Distribution

a. Timing of the distribution campaigns

Three studies [SR03, SR06, SR09] discussed findings related to the timing of the distribution campaigns. In India [SR03], campaigns failed to initiate on the scheduled day and were delayed. When this occurred compliance also decreased because the advertising in newspapers had already occurred and the community was not informed of a delay.

In Ghana [SR06], MDA campaigns sometimes conflicted with other public health campaigns, cocoa harvesting time, or the small-scale gold mining season. In these instances, it was more difficult to recruit distributors, as they preferred to take the jobs that paid better.

In Tanzania [SR09], distribution, in some instances, was delayed due to a late release of funds or medications. This led the campaigns to coincide with the rainy seasons (when farmers are away) or Ramadan (where drugs can only be consumed after dark).

Key message:

Studies found that MDA campaigns should be planned around local community events such as harvest, other public health campaigns and religious or national holidays in consultation with the community and implemented as advertised.

b. Length of the campaign

Linked to findings about the timing of campaigns were findings about the duration. All studies found that the duration of the campaigns in their settings was too short. Campaign duration ranged from 1-7 days across the study sites. In Tanzania [SR09], the community directed approach to MDA says

that each community should decide on the timing and duration for distribution that fits their context. However, the NTD control program based in Dar es Salaam decided on a duration of three days for all contexts. Distributors argued this was too little time to reach everyone. In urban areas, there were too many houses to visit in three days. In rural areas, the distance between the houses was too far. This time crunch was exacerbated when campaigns happened during the wet season when farmers were out at their fields and physical access to many areas becomes difficult.

"One day I came back home at eight in the evening while I started working since six in the morning until half past six in the evening, because I suspected people would be asked about the distribution and they would say they were not reached, and so my work would be seen [as] poor. The other constraint is that the distribution was done during the rainy season when many people were at their fields protecting their crops. If this was done during the dry season, we would cover … the people." (Female distributor in Lindi Urban)[SR09]

Accessibility was also raised as an issue in Ghana [SR06]. This study mentioned the same reasons as the study from Tanzania (rainy season and population growth) but added the inaccessibility of some villages was also linked to the difficulty in accessing vehicles and motorcycles to deliver staff to more remote locations. They felt this had an impact on reporting, as there was a delay in collecting reports from the different stations.

Studies from Ghana [SR06], India [SR07] and Kenya [SR12, SR13] all found that drug distributors believed the number of days allocated to distribute the drugs was too little, leading to lower rates of uptake. In Ghana [SR06] and Kenya [SR12, SR13] distributors believed that longer campaigns would allow them to reach more households and adequate time to finish their reporting duties.

Only one study in India [SR02] found that some doctors wanted to limit the MDA campaigns to one day in order to minimize the lower rates of compliance on subsequent days due to adverse reactions.

Key message:

Studies found that the majority of health workers and community drugs distributors interviewed believed that the MDA campaigns were too short and did not provide enough time to reach every household.

c. Distribution locations

Five studies [SR08, SR09, SR11, SR13, SR14] presented findings linked to the perceptions of the location in which drugs were distributed. In most locations, drugs were distributed in public settings and door-to-door distribution campaigns. In Tanzania [SR09] and Kenya [SR13] perceptions of house-to-house distribution were presented. In Kenya [SR13] participants were satisfied with this

form of distribution but felt that the duration of the campaigns meant that every house was not reached. It also allowed families to take the medications together.

‘‘This method of distributing drugs door- to- door is just good because each and every household will be visited and the choice of taking drugs will remain to be of the household head and even the community members want it that way because they think that is what is best.’’ (60 year old male Village Elder (opinion leader) from Barani sub-location)[SR13]

In American Samoa [SR08] and Papua New Guinea [SR14] there was a preference for drug distribution to follow religious services as this was when most of the community members were gathered together.

In American Samoa [SR08] house-to-house distribution was discontinued in 2003 and a focus on distribution in locations where people naturally gathered such as schools, place of employment, churches and the airport became the focus. There was less of a focus on distribution in public places like the market as health workers felt people did not want to be disturbed during their errands. Nurses interviewed preferred the house-to-house distribution as it provided a more personal interaction with people; however, they understood the logistical and time limitations that went with that form of distribution.

In Indonesia [SR11], participants felt that when distribution occurred in public settings, such as after a religious service, there was increased public pressure to comply as you did not want to be seen as the only one not swallowing the tablets.

Key message:

Studies found that in general, door-to-door distribution was accepted and that some communities preferred distribution at religious events and services.

d. Distributors

Four studies from Kenya [SR12, SR13] and Tanzania [SR09, SR10] discussed findings related to those distributing medications during MDA campaigns. In both settings, distributors spoke of their reception in the community. In some cases this was negative and in others positive. It was important to community members that the distributor was someone they knew and not a stranger [SR09, SR12]. In Tanzania, some distributors and community members believed that health workers should distribute the drugs. A distributor felt that a health worker could do a better job in educating the community:

“We have tried to educate them [fellow community members] and few have taken drugs. Maybe doctors and nurses will do better.” (Distributor, Tanzania)[SR09]

Some community members expressed a preference for a health worker to distribute the medications. They did not trust that someone with no health care training could do the job properly. Some refused to take the tablets in this case [SR09, SR10].

Distributors in both Kenya and Tanzania believed that the community should be better informed about the campaign, its benefits and rationale before the campaign start. They felt that they spent a lot of time explaining and convincing [SR10, SR13]. Sometimes this lack of information about the campaign led residents to feel surprised or intimidated when a distributor showed up at their house [SR09].

In Tanzania, some distributors felt an obligation to make people take the drugs. Sometimes this led to pressure and negotiations [SR09].

Key message:

Studies found that in many instances it was important for the community member to know the person distributing the drugs. In some instances, community members preferred when health workers, whom they believed to be more competent to conduct the task due to their medical training, distributed the drugs.

e. Supervision during campaigns

Health workers were most often employed to supervise the drug distribution and support CDDs with varying levels of engagement (13, SR09, SR12, SR13]. In the Philippines, it was reported that when the health officer was present during campaigns coverage increased [SR01]. In Tanzania, health workers initiated the MDA campaigns with traditional leaders and oversaw the distribution of drugs. In some cases, health workers were more actively involved walking with the CDDs during distribution. They often felt strongly about compliance and thought it was their duty to exert some pressure to get people to take the tablets.

“Oh, yes some of them did not accept…, so distributors would tell us ‘this house has refused’. We then educated [the household]: ‘do you know the reason [why] you are given these drugs? Do you know that the government is not foolish to bring these drugs? Do you know about these neglected diseases?’ These people are used to threats, so we told them: ‘very soon you will notice that your legs are swollen’, and in these places, people have seen these, so they know about mosquitoes and they have been bitten by mosquitoes for several years, so they accept to take drugs’.” (Health Worker in Lindi Urban)[SR09]

f. Reporting

Only two studies mentioned findings concerning reporting during MDA campaigns. In Kenya, a number of distributors said that they had been supported in record keeping by community members [SR12]. In Ghana [SR06], distributors often had low levels of literacy, which made completing the

record keeping difficult and lead to delays. They calculated manually which often led to inaccuracies in the summaries. Distributors wanted calculators to make their work easier.

“When you give the drugs, example you give Ivermectin 3 and Albendazole 1, the books are big, the population is big so you have to calculate a lot. And that alone can take about 2 days. We have to calculate a lot and it makes the work difficult.” (CHV, FGD, Ahanta West)[SR06]

This lead to more work for supervisors who had to double check or finish calculations, affecting accuracy and leading to further delays in reporting.

4.2.11 External communication

a. Mass media

Many studies (13, SR03, SR04, SR08, SR09, SR13, SR14] referred to mass media as a communication tool for MDA programs. Television and radio public service announcements, ranging from educational videos to announcements of date and time, were used to inform communities about upcoming campaigns (13, SR03, SR08, SR09, SR13, SR14]. In India [SR03, SR04], mass media had a negative effect on uptake when local newspapers reported exaggerated side effects, such as death, from the MDA program.

b. Content

A number of studies addressed the lack of information or lack of wanted content within the information that was received (13, SR03, SR04, SR09-SR13]. The findings highlight that community members wanted more information about side effects [SR04] and the benefits and rationale for taking the drugs [SR09].

Health workers in the Philippines explained that the information they received to distribute to communities focused on LF the disease and did not provide information about the MDA program. This information was not provided in local languages, which was a barrier to understanding the content. A lack of information about the MDA program was also reported in Kenya [SR13].

In Tanzania [SR09], the message communicated to the public aimed to inform the community that the tablets being distributed were meant to treat the infection that caused both hydrocele and elephantiasis. However, many of the drug distributors had misconceptions about the cause and transmission of LF and were communicating misinformation to the public. This demonstrated a break down in the training and communication strategy [SR09].

Only one study clearly described the content of a communication intervention used in a community setting to distribute information about MDA [SR08]. King 2011 [SR08] described a public service announcement that was developed in American Samoa for television and radio to increase awareness of LF and the need for all persons to be treated in MDA. It focused on the lack of knowledge about the infection and the disease in the community and the purpose of the MDA program.

c. Frequency

Two studies mentioned findings related to the frequency of communicating about MDA [SR09, SR13]. Both of these studies found that participants wanted more frequent messaging to occur in the run up to MDA campaigns so that communities would be more aware when distributors arrived at their homes.

d. The role of health workers in communicating to the public

Two studies [SR01, SR09] described the important roles that health workers play in communicating about LF and MDA to communities. In the Philippines [SR01], health workers were found to be the major source of information about LF and MDA for community members. The authors found that their active and sustained participation would be vital in the long-term success of the program. However, health workers felt like they needed more support from local government to make the program succeed.

In Tanzania [SR09], it was the health workers responsibility to reach out to communities to discuss LF and underline the importance of collaboration between health workers and communities during MDA campaigns. The health worker clearly defined and explained the roles and responsibilities of the various organisations involved in MDA and supported the community in the planning and implementation of the MDA campaign.

e. Information, education and communication (IEC) materials

Three studies mentioned IEC strategies (13, SR03, SR13]. In the Philippines, NGO staff were very involved in IEC activities but knew little of the rationale or benefits of the MDA [SR01]. In India, the authors discovered that in communities where IEC activities had been better, communities understood the benefits of the program and were more aware of the side effects. In these communities, coverage and compliance rates tended to be higher [SR03].

Njomo 2014 [SR13] provided a more detailed account of IEC activities in Kenya. They found that CDDs wanted IEC materials available in the local language with frequent reminders by town announcers in the days before the campaign to ensure community awareness. They felt that the posters in use had adequate information and a good use of visuals but that more detail was needed surrounding the cause of the disease. Opinion leaders in this setting expressed the need for a combination of IEC interventions, such as posters, town announcers, banners and artistic performances, to increase community awareness. The preferred modes of awareness creation by all study participants included:

- posters
- churches and mosques
- schools
- local radio stations
- road shows
- newspaper
- drama
- District Commissioners and District Officers
- theatre groups
- loudspeakers
- chief's meetings (barazas)

Key message:

Studies found that communities felt that they were not receiving enough information about MDA campaigns. They wanted more information about the benefits of and rationale for participating and the side effects from taking the tablets.

Studies found that communities wanted more frequent messaging about MDA campaigns delivered through a wider variety of locally preferred communication modes.

4.2.12 Community participation

A number of studies discussed community participation in various facets of MDA campaigns [SR03, SR05, SR08, SR09, SR12-SR14]. All of the studies found that community involvement was a key element in their success. Two studies reported limited or inadequate community involvement as a hindrance to MDA campaigns [SR03, SR12]. In India [SR03], increased community involvement lead to higher coverage and compliance rates. In the Dominican Republic [SR05], increased community involvement led to increased community knowledge and a quicker completion of distribution.

In American Samoa [SR08], Kenya [SR13] and Papua New Guinea [SR14] the preferred method of community involvement was through religious organisations. In Kenya [SR13] and Papua New Guinea [SR14] the community thought that the religious groups could be better utilised to communicate about MDA campaigns and aid in distribution. In American Samoa [SR08] a concerted effort had been made to involve church leaders in the communication about MDA campaigns and the distribution of tablets after religious services. The church leaders believed that their involvement was important and wanted to be involved in the MDA campaigns. To reach people who did not attend religious services tablets were also distributed at schools, places of employment, bingo halls, the airport and were available at all health stations.

In Tanzania [SR09], the central focus of community involvement was through social mobilisation. The aim of social mobilisation is to engage communities to a point where they can sustain programs and adhere to the strategies being used without external support. Responsibility for mobilisation is shared by local government representatives, health workers and community representative who work together to inform the community before the campaign using multiple strategies.

Key message:

All of the studies included found that community involvement in the planning and implementation of MDA campaigns was important in ensuring their success.

Table 11 Key messages – feasibility scoping review.

Community members
Studies found that: 1. In general, communities lacked knowledge about the cause and mode of transmission of LF and that hydrocele and elephantiasis had the same cause.
2. When communities understood the benefits and aims of MDA campaigns for the elimination of LF and the potential side effects of the tablets they were more open to and accepting of the MDA campaigns.
3. Participation in MDA campaigns tended to be higher when; communities were involved in the planning and implementation of the campaign, the disease (LF) and MDA program are considered a priority in the community, and those distributing the drugs, whether health workers or community drug distributors, are trusted in the community setting.
4. Participation in MDA campaigns tend to decrease when; side effects are experienced or feared, when there is a lack of information about LF, the tablets or the campaign available to community members or when communities believe rumours about the tablets or campaign that raise doubts and suspicion
Providers of care: Health workers and drug distributors
Studies found that: 5. Often health workers had a good understanding that LF was a problem in their setting, of the cause and mode of transmission of LF and that hydrocele and elephantiasis had the same cause. However, this knowledge was not as prevalent amongst community drug distributors who often had misconceptions surrounding the topic.
Health systems factors
Studies found that: 6. The involvement of and support from all levels of healthcare services in the MDA campaigns was important for the success of the program.
7. There was a lack of supervision of community drug distributors during MDA campaigns.
8. In general, there was an insufficient number of people involved in distributing tablets during MDA campaigns.
9. In general, community drug distributors did not receive adequate training to fulfil their duties during MDA campaigns.
10. Incentives were important for drug distributor motivation when they were perceived as adequate and a demonstration of the appreciation of their time and effort. However, if the remuneration was perceived as not enough or less than what was offered in other public health programs it influenced distributor motivation and could lead to leaving the program.
11. Access to and the provision of treatment for side effects during MDA campaigns could help to increase coverage and compliance.
12. MDA campaigns should be planned around local community events such as harvest, other public health campaigns and religious or national holidays in consultation with the community and implemented as advertised.
13. The majority of health workers and community drugs distributors interviewed believed that the MDA campaigns were too short and did not provide enough time to reach every household.
14. In general, door-to-door distribution was accepted and some communities preferred distribution at religious events and services.
15. In many instances, it was important for the community member to know the person distributing the drugs. In some instances, community members preferred when health workers, whom they believed to be more competent to conduct the task due to their medical training, distributed the drugs.
16. Communities felt that they were not receiving enough information about MDA campaigns. They wanted more information about the benefits of and rationale for participating and the side effects from taking the tablets.
17. Communities wanted more frequent messaging about MDA campaigns delivered through a wider variety of locally preferred communication modes.
18. Community involvement in the planning and implementation of MDA campaigns was important in ensuring their success.

5 Conclusions

5.1 Effectiveness and safety

- Effectiveness outcomes either showed no differences between groups or slightly favoured alternative drug regimens.
- MF clearance or prevalence in comparisons that involved only changes in the frequency of administration of drugs (DA and IA biannual versus annual) suggested no effect differences between groups.
- MF clearance or prevalence favoured intervention arms (or 'after' measurements) as compared to control arms (or 'before' measurements) in regiments comparing three versus two drugs (IDA versus DA or IA).
- Microfilarial density findings, as expected, were consistent with MF clearance or prevalence. Microfilarial density reductions were more remarkable in triple drug interventions but there were no differences comparing biannual versus annual regimens.
- Other outcomes were less often reported. Adult worm nest clearance favoured triple drug regimens but showed no differences comparing biannual versus annual regimens. CFA prevalence, however, suggested significant reductions in the study comparing biannual versus annual regimens in Indonesia, but hardly any effect in Liberia and Côte d'Ivoire.
- Most of the data for safety came from the ongoing DOLF studies. None of the pooled estimates of the overall cohorts or done by participants subgroups or infection status suggested significant differences between the IDA and DA study arms. The only exception was the pooled estimate of 'any adverse event in participants FTS positive, where the estimate favoured the control group (less adverse events), despite the small number of adverse events in both groups.
- Other adverse events estimates comparing biannual versus annual AD, showed no differences between groups.
- Evidence has to be interpreted with caution given the GRADE quality of evidence assessments. The low GRADE of evidence has been generally attributed to the risk of bias of the underlying studies but also to the low number of studies with small sample sizes, except for the safety data of the DOLF ongoing studies.

5.2 Feasibility

The following questions, derived from the key messages, may help programme managers and other stakeholders to assess whether the MDA campaigns they are planning adequately address the issues that are important to communities and drug distributors discussed in this synthesis.

1. Has an attempt been made to involve local community groups in planning, announcing and distribution during MDA campaigns?
2. Has an attempt been made to ensure that all levels of the health services are involved in and supportive of the planning and implementation of MDA campaigns?
3. Has an attempt been made to tailor information about MDA campaigns to each community, area and or setting?
4. Has an attempt been made to ensure that information about MDA campaigns (date, time, location, duration, medication and side effects) is communicated to communities in good time and often before the campaign begins?
5. Has an attempt been made to ensure that information about MDA campaigns is being provided to local communities in multiple formats using clear and simple text and photos in a local language?
6. Has an attempt been made to ensure that information about the MDA campaign is available at a wide range of health service and community settings? Is it possible to have discussions about LF and MDA in these settings?
7. Has an attempt been made to ensure that communication programs are providing clear information on the cause and mode of transmission of LF? That hydrocele and elephantiasis are both caused by the same parasite?
8. Has an attempt been made to ensure that health workers and drug distributors are able to provide clear and correct answers to questions in the communities where they work in an open and respectful way?
9. Has an attempt been made to adjust MDA communication strategies to respond to media stories, rumours and negative publicity about MDA in order to respond to community questions and concerns that these stories may have raised?
10. Has an attempt been made to ensure that adequate training is being given to drug distributors on how to communicate effectively with stakeholders, the rationale and benefits of the MDA campaign, cause and mode of transmission of LF and side effects of the medications?
11. Has an attempt been made to offer incentives to drug distributors? If yes, how do they compare to the incentives given by other public health programs?
12. Has an attempt been made to ensure that local events and context have been taken into consideration when planning the dates for and duration of MDA campaigns? The location where drugs will be distributed?
13. Has an attempt been made to ensure that drug distributors are known and trusted people in the community?
14. Has an attempt been made to ensure that community members have support and access to health services to deal with side effects of the medications?
15. Has an attempt been made to ensure that adequate human resources and financial support are being given to the MDA campaigns in a timely manner?

ANNEXES

Annex 1. Generic search strategy for effectiveness and safety review

1 Elephantiasis, Filarial/di, dt, pc [Diagnosis, Drug Therapy, Prevention & Control] (1439)
2 ((lymphatic or bancroft* or filarial) adj3 (elephantias* or filarias*)).ti,ab,kw. (3495)
3 exp Wuchereria/ (2941)
4 exp Brugia/ (2639)
5 (wuchereria or brugia).ti,ab,kw. (4571)
6 or/1-5 (7644)
7 Albendazole/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity] (3457)
8 Diethylcarbamazine/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity] (1603)
9 Ivermectin/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity] (4051)
10 (albendazole* or diethylcarbamazine* or DEC or ivermectin*).ti,ab,kw. (17817)
11 Anthelmintics/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity] (9986)
12 Filaricides/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity] (1229)
13 drug therapy/ or drug therapy, combination/ (196399)
14 (albendazole* or diethylcarbamazine* or DEC or ivermectin* or "mass drug administration" or ("combin* drug" adj (therapy or administration)) or filaricid* or anthelmint* or antifilarial).ti,ab,kw. (26997)
15 or/7-14 (229554)
16 randomized controlled trial.pt. (508190)
17 controlled clinical trial.pt. (98209)
18 multicenter study.pt. (256767)
19 (randomis* or randomiz* or randomly allocat* or random allocat*).ti,ab. (575857)
20 groups.ab. (1801457)
21 (trial or multicenter or multi center or multicentre or multi centre).ti,ab. (621748)
22 (intervention* or controlled or control group or compare or compared or (before adj5 after) or (pre adj5 post) or pretest or pre test or posttest or post test or quasiexperiment* or quasi experiment* or evaluat* or effect or impact or time series or time point? or repeated measur*).ti,ab. (8910155)
23 or/16-22 (9754754)
24 exp Animals/ (23119563)
25 Humans/ (18265813)
26 24 not (24 and 25) (4853750)
27 review.pt. (2443558)
28 meta analysis.pt. (86667)
29 news.pt. (198675)
30 comment.pt. (735376)
31 editorial.pt. (458558)
32 cochrane database of systematic reviews.jn. (17180)
33 comment on.cm. (735376)
34 (systematic review or literature review).ti. (94331)
35 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (8355836)
36 23 not 35 (6975053)
37 6 and 15 and 36 (806)
38 limit 37 to yr="2002 -Current" (489)

Annex 2. Generic search strategy for scoping qualitative review

1 (perception* or perceiv* or opinion* or attitude* or view* or experienc* or sceptic* or skeptic* or dilemma* or "social mobilisation" or "social mobilization" or complian* or refus* or feeling* or impression* or belief* or trust or accept* or knowledge or comprehension or understanding or aware*).ti,ab,kw. (3389596)
2 Patient Satisfaction/ (75396)
3 health behavior/ or patient compliance/ or medication adherence/ or no-show patients/ or patient dropouts/ or treatment refusal/ (137860)
4 community networks/ or social support/ or social norms/ (74256)
5 attitude to health/ or health knowledge, attitudes, practice/ (179641)
6 Family Characteristics/ (24737)
7 Leadership/ (39006)
8 consumer participation/ or patient participation/ (41941)
9 Consumer Behavior/ or Consumer Advocacy/ or Consumer Organizations/ (25563)
10 "Patient Acceptance of Health Care"/ (42020)
11 Social Perception/ (22193)
12 or/1-11 (3693612)
13 Elephantiasis, Filarial/di, dt, pc [Diagnosis, Drug Therapy, Prevention & Control] (1444)
14 (elephantias* or filarias*).ti,ab,kw. (8258)
15 exp Wuchereria/ (2942)
16 exp Brugia/ (2640)
17 (wuchereria or brugia*).ti,ab,kw. (4636)
18 or/13-17 (11390)
19 Albendazole/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity] (3464)
20 Diethylcarbamazine/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity] (1603)
21 Ivermectin/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity] (4057)
22 (albendazole* or diethylcarbamazine* or DEC or ivermectin*).ti,ab,kw. (17860)
23 Anthelmintics/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity] (9996)
24 Filaricides/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity] (1231)
25 drug therapy/ or drug therapy, combination/ (197079)
26 (albendazole* or diethylcarbamazine* or DEC or ivermectin* or "mass drug administration" or ("combin* drug" adj (therapy or administration)) or filaricid* or anthelmint* or antifilarial).ti,ab,kw. (27060)
27 or/19-26 (230304)
28 12 and 18 and 27 (378)
29 qualitative research/ or community-based participatory research/ (40844)
30 (qualitative or ethno$ or emic or etic or phenomenolog$ or hermeneutic$ or heidegger$ or husserl$ or colaizzi$ or giorgi$ or glaser or strauss or van kaam$ or van manen or constant compar$).ti,ab. (219503)
31 Focus groups/ or Interview/ or Interviews as Topic/ or Questionnaires/ or Self-report/ or narration/ or "surveys and questionnaires"/ or health care surveys/ (550518)
32 (focus group$ or grounded theory or narrative analys$ or lived experience$ or life experience$ or theoretical sampl$ or purposive sampl$ or ricoeur or spiegelberg$ or merleau or metasynthes$

or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$ or maximum variation or snowball or questionnaire*).ti,ab. (474134)
33 ((thematic$ adj3 analys$) or (content analy$ or field note$ or fieldnote$ or field record$ or field stud$) or (participant$ adj3 observ$) or (nonparticipant$ adj3 observ$) or (non participant$ adj3 observ$)).ti,ab. (56598)
34 (semi-structured or semistructured or structured categor$ or unstructured categor$ or action research or (audiorecord$ or taperecord$ or videorecord$ or videotap$) or ((audio or tape or video$) adj5 record$) or interview* or quasi-experiment* or (case adj stud*)).ti,ab. (418805)
35 (collaborat* or consultat* or experience or involve* or narrative* or opinion* or participat* or partner* or perspective* or story or stories or view* or voice*).ti,ab. (3581783)
36 or/29-35 (4391946)
37 limit 28 to "qualitative (maximizes sensitivity)" (111)
38 28 and 36 (186)
39 37 or 38 (228)

Annex 3. List of included studies in the effectiveness and safety review.

1) Tafatatha, T.T., et al., *Randomised controlled clinical trial of increased dose and frequency of albendazole and ivermectin on Wuchereria bancrofti microfilarial clearance in northern Malawi.* Trans R Soc Trop Med Hyg, 2015. **109**(6): p. 393-9.
2) Thomsen, E.K., et al., *Efficacy, Safety, and Pharmacokinetics of Coadministered Diethylcarbamazine, Albendazole, and Ivermectin for Treatment of Bancroftian Filariasis.* Clin Infect Dis, 2016. **62**(3): p. 334-341.
3) Dembele, B., et al., *Use of high-dose, twice-yearly albendazole and ivermectin to suppress Wuchereria bancrofti microfilarial levels.* Clin Infect Dis, 2010. **51**(11): p. 1229-35.
4) Kar, S.K., et al., *A randomized controlled trial of increased dose and frequency of albendazole with standard dose DEC for treatment of Wuchereria bancrofti microfilaremics in Odisha, India.* PLoS Negl Trop Dis, 2015. **9**(3): p. e0003583.
5) El Setouhy, M., et al., *A randomized clinical trial comparing single- and multi-dose combination therapy with diethylcarbamazine and albendazole for treatment of bancroftian filariasis.* Am J Trop Med Hyg, 2004. **70**(2): p. 191-6.
6) Kar, S.K., et al., *A clinical trial of single dose DEC and Albendazole showing reversal of lymphatic pathology in children with Wuchereria bancrofti infection in Odisha, India.* PLoS Negl Trop Dis, 2017. **In press.**
7) Bjerum, C.M., Aboulaye, M., Ouattara, A.F., Kouadio, O., Marius, V.K., Andersen, B., Kazura, J.W., Weil, G.J., Koudou, B.G., King, C.L. *A randomized clinical trial comparing the effects of a single dose of ivermectin plus diethylcarbamazine plus albendazole with standard treatment of ivermectin plus albendazole for lymphatic filariasis in Côte d'Ivoire*. Submitted for publication; 2017.
8) King, C.L., Suamani, J., Sanuku, N., Cheng, J., Satofan, S., Mancuso, B., Lombore, B., Siba, P.M., Weil, G.J., Kazura, J.W., *Superior Efficacy of Co-Administered Single Dose Therapy with Diethylcarbamazine, Albendazole, and Ivermectin versus Standard Therapy (Diethylcarbamazine with Albendazole) for Bancroftian Filariasis in Papua New Guinea*. Submitted for publication; 2017.
9) Pion, S.D., et al., *Effect of 3 years of biannual mass drug administration with albendazole on lymphatic filariasis and soil-transmitted helminth infections: a community-based study in Republic of the Congo.* Lancet Infect Dis, 2017.

Additional references and data:

DOLF-ongoing / Weil G, Fischer PU. Interim report of MDA optimisation studies. 2017 [Community randomized studies of IDA vs DA mass distribution for elimination of LF. ongoing studies].

Weil, G.J., King, C.L. *Death to Onchocerciasis and Lymphatic Filariasis (DOLF) Triple Drug Therapy for Lymphatic Filariasis. Community safety studies.* 2016, ClinicalTrials.gov NCT02899936.

Lemoine, J.F., Dubray C. *Death to Onchocerciasis and Lymphatic Filariasis Triple Drug Therapy for Lymphatic Filariasis. Community safety studies in Haiti (DOLF-HAITI).* 2016, ClinicalTrials.gov NCT02899936.

Jambulingam, P., Krishnamoorthy, K. *Death to Onchocerciasis and Lymphatic Filariasis Triple Drug Therapy for Lymphatic Filariasis. Community safety studies in India (DOLF-INDIA).* 2016, ClinicalTrials.gov NCT02899936.

Supali, T., Djuardi, Y. *Death to Onchocerciasis and Lymphatic Filariasis Triple Drug Therapy for Lymphatic Filariasis. Community safety studies in Indonesia (DOLF-INDONESIA).* 2016, ClinicalTrials.gov NCT02899936.

Siba, P., Robinson, L., *Death to Onchocerciasis and Lymphatic Filariasis Triple Drug Therapy for Lymphatic Filariasis. Community safety studies in Papua New Guinea (DOLF-PNG).* 2016, ClinicalTrials.gov NCT02899936.

Supali, T., Djuardi, Y., Kaisar, M., Stefanie, D., Weil, G.J., Fischer, P. *Impact of once and twice yearly mass drug administration on bancroftian filariasis and soil transmitted helminth infection in central java, Indonesia.* American Journal of Tropical Medicine and Hygiene, 2015. **93**(4 Supplement, Abstract 151 (Clinicaltrials.gov NCT01905423)).

Bolay, F.K., Fischer, P.U., Weil, G.J. *Mass Drug Administration for Lymphatic Filariasis and Onchocerciasis for Liberia (DOLF-LIBERIA)*. 2013, Clinical Trials.gov NCT01905436.

Meite, A., Weil, G.J., Fischer, P.U. *Optimization of Mass Drug Administration With Existing Drug Regimens for Lymphatic Filariasis and Onchocerciasis for Ivory Coast (DOLF-CIV)*. 2014, Clinicaltrials.gov NCT02032043.

Annex 4. List of excluded studies and reasons for exclusion

Table 12. Excluded studies and reasons for exclusion.

	Reference	Reason for exclusion
1	Britto 2015	Not relevant comparison
2	CTRI/2012/02/002467 2012	Not relevant comparison; no relevant outcome
3	DOLF MDA CIV DOLF MDA Study Cote d'Ivoire	Not relevant comparison; no relevant outcome
4	DOLF MDA INDONESIA Supali1 2015	Included in IDN 3157
5	DOLF MDA INDONESIA Supali2	Not relevant comparison; no relevant outcome
6	DOLF MDA LIBERIA 2014	Included in IDN 3157
7	DOLF MDA PNG DOLF MDA study PNG	Not relevant comparison; no relevant outcome; included in 3157
8	DOLF SAFETY HAITI Triple drug	Included in IDN 3157
9	DOLF SAFETY INDIA Triple-drug 2016	Included in IDN 3157
10	DOLF SAFETY INDONESIA Triple drug	Included in IDN 3157
11	DOLF SAFETY PNG Triple drug	Included in IDN 3157
12	Dwibedi / Kar | Jonathan	Duplicate
13	Fischer 2014	Wrong study design
14	French 2010	Not relevant comparison; duplicate
15	Hoti 2012	Not relevant comparison
16	Jonathan DOFL Kazura/King	Not relevant comparison; no relevant outcome
17	Jonathan DOLF Cking	Not relevant comparison; no relevant outcome
18	Jonathan DOLF Cote d'Ivoire	Not relevant comparison; no relevant outcome
19	Jonathan DOLF Liberia 1 and 2	Not relevant comparison; no relevant outcome
20	King 2016	Not relevant comparison; no relevant outcome
21	NCT01213576 2010	Not relevant comparison; no relevant outcome
22	NCT01905436 = DOLF Liberia 2013	Duplicate
23	NCT01975441 2013	Duplicate
24	Pion Single arm	Not relevant comparison; no relevant outcome
25	Siba 2013	Not relevant comparison; no relevant outcome
26	Thomsen 2014	Not relevant comparison; no relevant outcome
27	Thomsen 2015	Not relevant comparison; no relevant outcome
28	University-Hospitals-Cleveland 2014	Not relevant comparison; no relevant outcome
29	Washington-University 2014	Not relevant comparison; no relevant outcome
30	Washington-University 2016	Duplicate
31	Weerasooriya, 2009	Not relevant comparison
32	Weil 2016	Not relevant comparison; no relevant outcome
33	Yongyuth, 2009	Not relevant comparison

Annex 5. Characteristics of included studies

Table 13. Characteristics of included studies.

Reference	Country	Geographical scope	Year start	Year end	Participants age (years)			Study design	Individuals	Clusters
Tafatatha 2015	Malawi	Sub-national	2009	2012	18	to	55	RCT	70	16
Thomsen 2016	Papua New Guinea	Sub-national	NA	NA	18	to	60	RCT	24	2
Dembele 2010	Mali	Sub-national	2007	NA	18	to	62	RCT	42	2
Kar 2015	India	Sub-national	2009	2012	18	to	55	RCT	104	1
El Setouhy 2004	Egypt	Sub-national	NA	NA	18	to	NA	RCT	NA	1
Kar 2017	India	Sub-national	2009	2014	5	to	18	RCT	102	12
Bjerum 2016	Côte d'Ivoire	Sub-national	2015	NA	NA		NA	RCT	NA	10
King 2017	Papua New Guinea	Sub-national	2014	NA	18	to	65	RCT	182	12
Pion single arm	Congo Rep	Sub-national	2012	2015	5	to	any age	Other without control	NA	1
DOLF SAFETY Triple-drug	Haiti, Indonesia, PNG, India	International	2016	2018	2	to	any age	RCT	20,000	4

Annex 6. Additional safety data (IDA versus DA)

Figure 3. Ivermectin, DEC and Albendazole (IDA) compared to DEC with Albendazole (DA) (onchocerciasis NOT co-endemic) – any adverse event by participants subgroup.

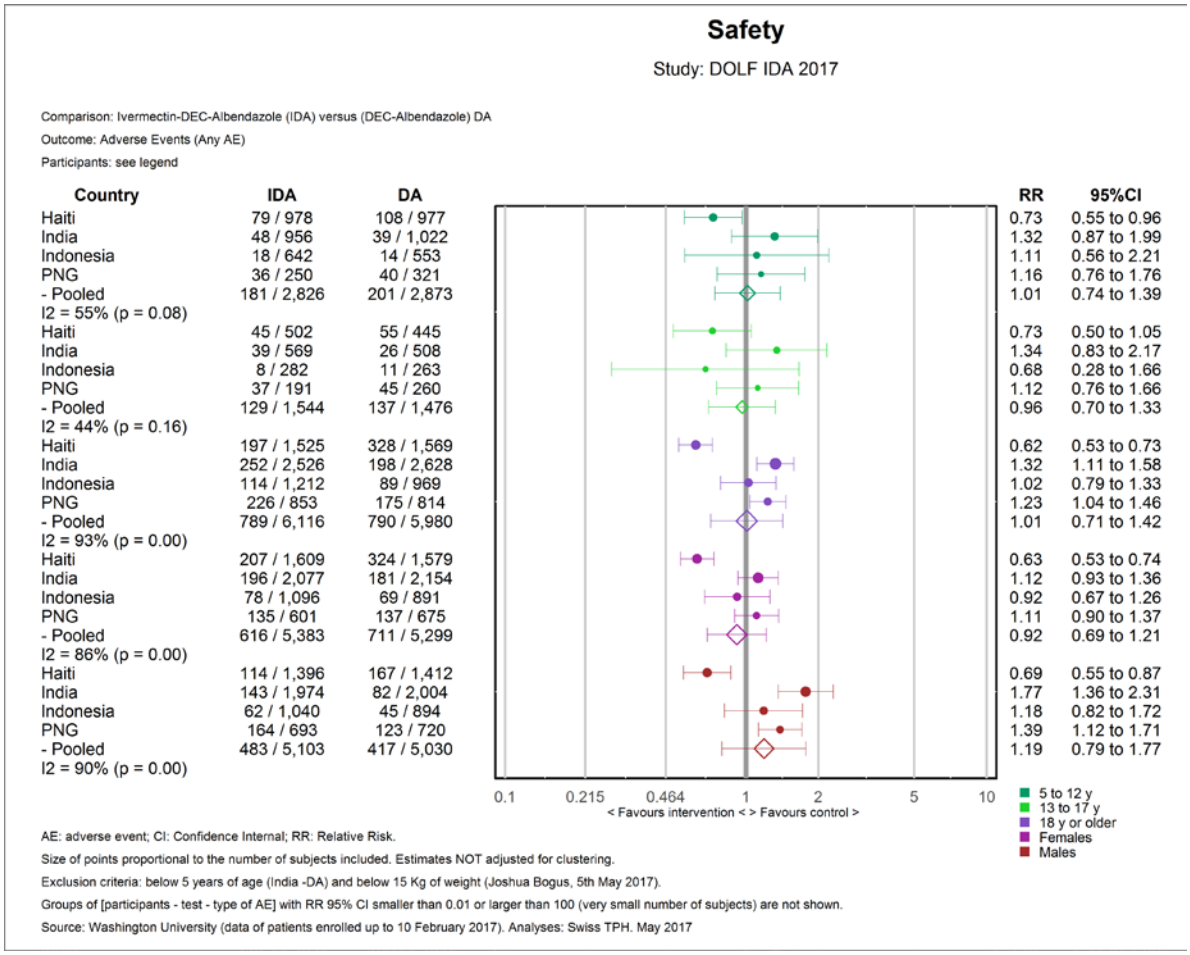


Figure 4. Ivermectin, DEC and Albendazole (IDA) compared to DEC with Albendazole (DA) (onchocerciasis NOT co-endemic) – any adverse event by infection status.

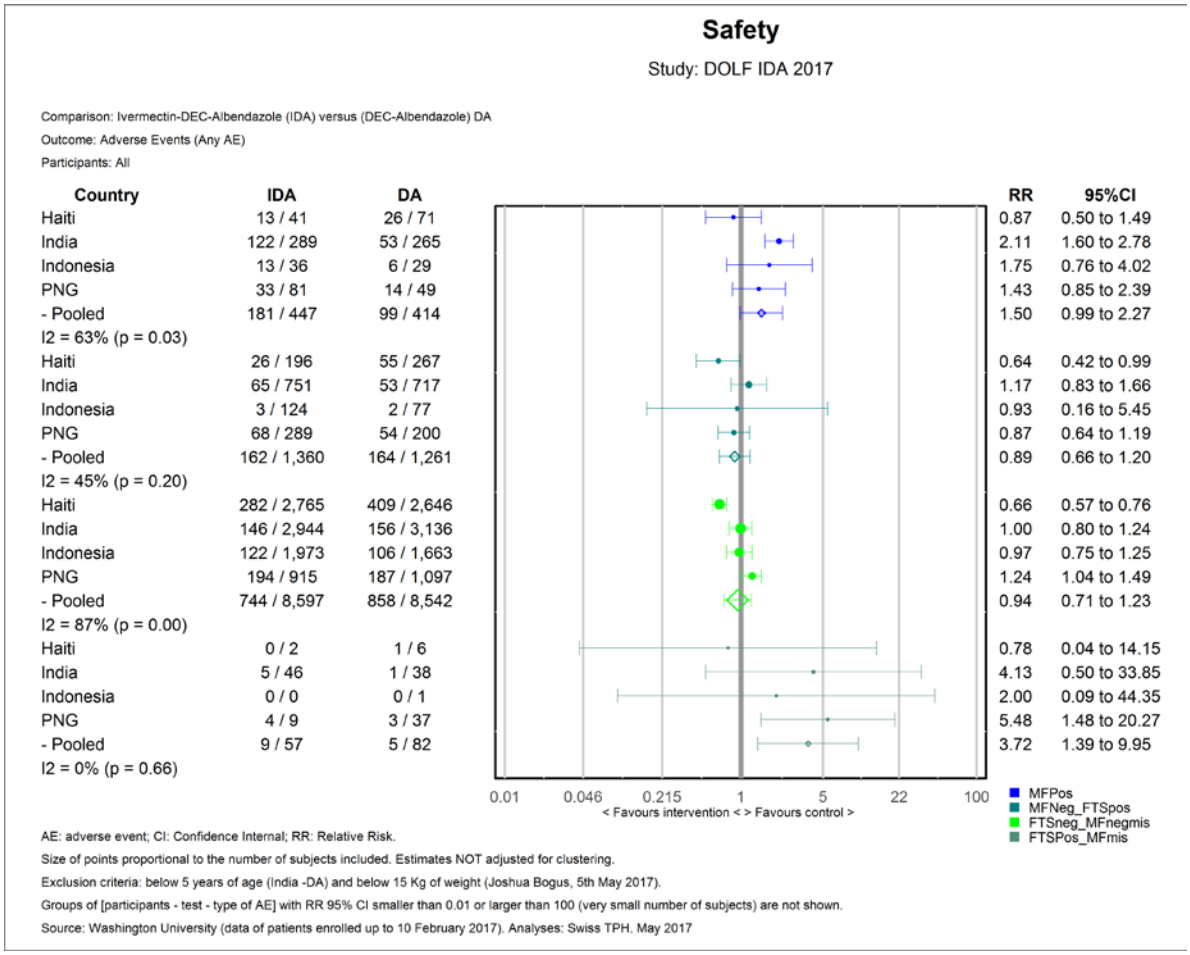


Figure 5. Ivermectin, DEC and Albendazole (IDA) compared to DEC with Albendazole (DA) (onchocerciasis NOT co-endemic) –grade 2 by participant subgroup.

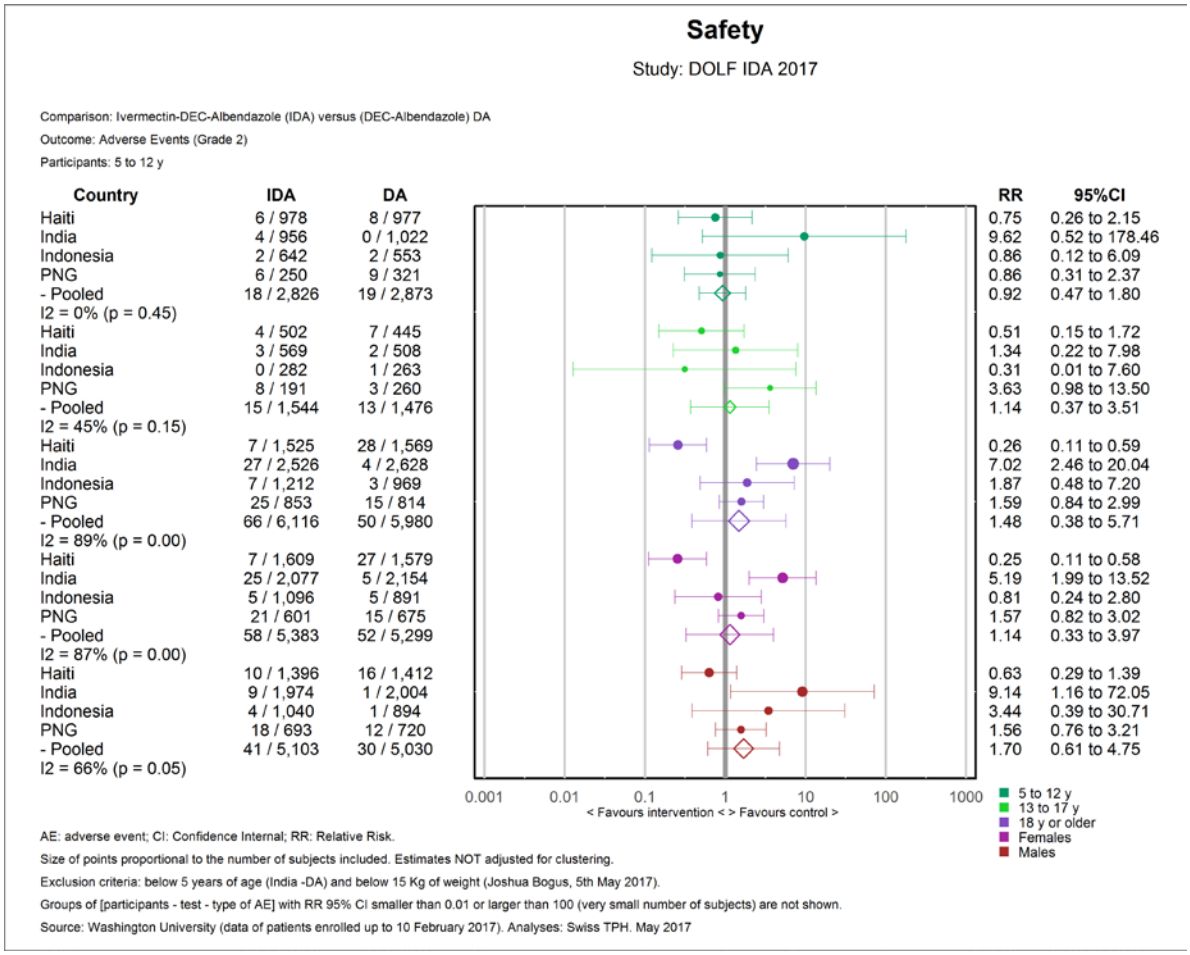


Figure 6. Ivermectin, DEC and Albendazole (IDA) compared to DEC with Albendazole (DA) (onchocerciasis NOT co-endemic) – grades 2 to 4 by infection status.

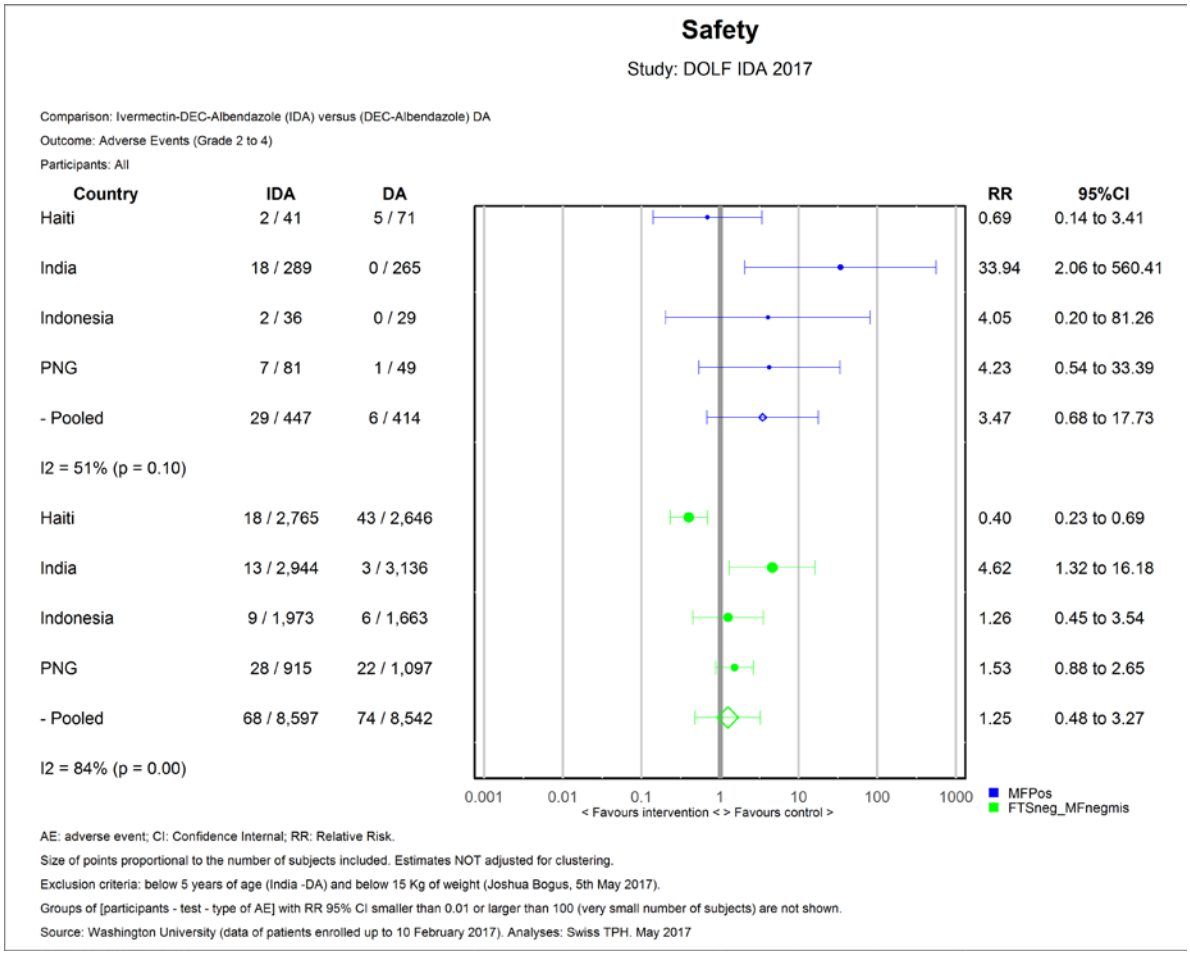
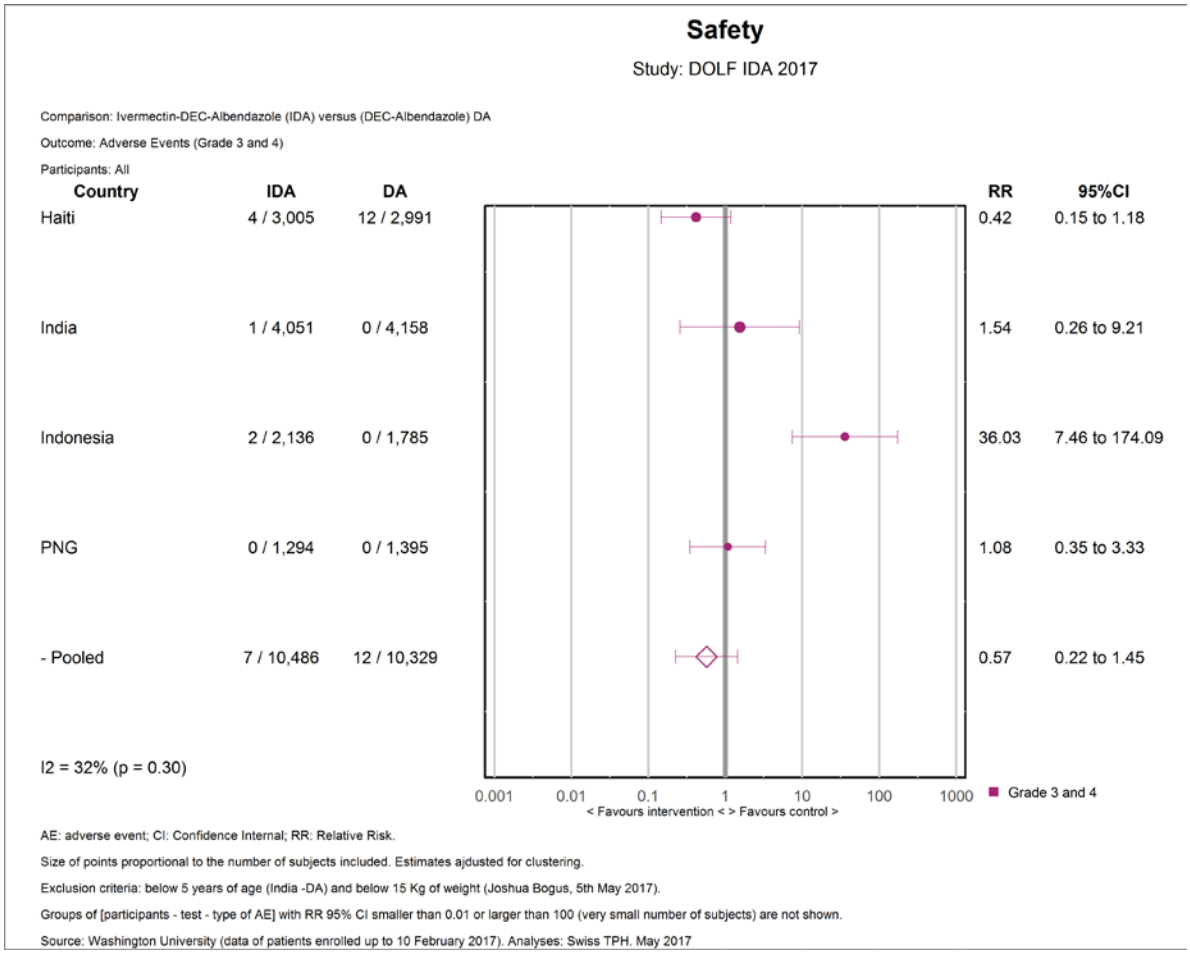


Figure 7. Ivermectin, DEC and Albendazole (IDA) compared to DEC with Albendazole (DA) (onchocerciasis NOT co-endemic) – grades 3 to 4.



Annex 7. GRADE Summary of findings (SOF) tables

Should IDA vs. DA be used for annual mass drug administration to eliminate lymphatic filariasis? Bibliography:											
Quality assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With DEC with albendazole (DA)	**With ivermectin, DEC and albendazole (IDA)**		**Risk with DEC with albendazole (DA)**	**Risk difference with ivermectin, DEC and albendazole (IDA)**
Complete microfilaria clearance (follow up: 24 months)											
121 (2 RCTs) [1,2]	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	33/61 (54.1%)	58/60 (96.7%)	**RR 1.75** (1.39 to 2.20)	541 per 1,000	**406 more per 1,000** (211 more to 649 more)
Microfilarial density (geometric mean) (follow up: 24 months)											
128 (2 RCTs) [1,2]	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	64	64	-	The mean microfilarial density (geometric mean) was **0**	Ratio of means **0.1 higher** (0.07 higher to 0.14 higher)
Circulating Filarial Antigen (CFA) prevalence (assessed with: Alere Filariasis Test Strip)											
116 (1 RCT) [2]	serious [a]	not serious	serious [d]	not serious	none	⨁⨁◯◯ LOW	57/58 (98.3%)	57/58 (98.3%)	**RR 1.00** (0.95 to 1.04)	983 per 1,000	**0 fewer per 1,000** (49 fewer to 39 more)
Serious Adverse Events (assessed with: cohort event monitoring)											

Should IDA vs. DA be used for annual mass drug administration to eliminate lymphatic filariasis? Bibliography:											
Quality assessment							Summary of findings				
20815 (4 RCTs) [3,e]	serious [f]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	3/10329 (0.0%) [e]	0/10486 (0.0%)	**RR 0.48** (0.08 to 2.90)	29 per 100,000 [e]	**15 fewer per 100,000** (27 fewer to 55 more)
Adverse Events Grade 3 and 4 (assessed with: cohort event monitoring)											
20815 (4 RCTs) [3]	serious [f]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	12/10329 (0.1%)	7/10486 (0.1%)	**RR 0.57** (0.22 to 1.45)	116 per 100,000	**50 fewer per 100,000** (91 fewer to 52 more)
Adverse events Grade 2 to 4 in communities with no prior MDA											
6610 (2 RCTs) [3]	serious [f]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	33/3180 (1.0%)	50/3430 (1.5%)	**RR 1.51** (0.96 to 2.39)	10 per 1,000	**5 more per 1,000** (0 fewer to 14 more)
Adverse events Grade 2 to 4 among MF positive persons (assessed with: cohort event monitoring)											
861 (4 RCTs) [3]	serious [f]	not serious	not serious	serious [g]	none	⊕⊕◯◯ LOW	6/414 (1.4%)	29/447 (6.5%)	**RR 3.47** (0.68 to 17.73)	14 per 1,000	**36 more per 1,000** (5 fewer to 242 more)
Any Adverse Events in MF positive (assessed with: cohort event monitoring)											
861 (4 RCTs) [3]	serious [f]	not serious	not serious	serious [g]	none	⊕⊕◯◯ LOW	99/414 (23.9%)	181/447 (40.5%)	**RR 1.50** (0.99 to 2.27)	239 per 1,000	**120 more per 1,000** (2 fewer to 304 more)
Adverse Events Grade 2 (assessed with: cohort event monitoring)											

Should IDA vs. DA be used for annual mass drug administration to eliminate lymphatic filariasis? Bibliography:											
Quality assessment							Summary of findings				
20815 (4 RCTs) [3]	serious [f]	serious	not serious	not serious	none	⊕⊕◯◯ LOW	82/10329 (0.8%)	99/10486 (0.9%)	**RR 1.27** (0.26 to 6.19)	8 per 1,000	**2 more per 1,000** (6 fewer to 41 more)
Any Adverse Events (assessed with: cohort event monitoring)											
21196 (4 RCTs) [3]	serious [f]	serious	not serious	not serious	none	⊕⊕◯◯ LOW	1138/10677 (10.7%)	1100/10519 (10.5%)	**RR 1.10** (0.67 to 1.78)	107 per 1,000	**11 more per 1,000** (35 fewer to 83 more)

CI: Confidence interval; **RR:** Risk ratio

a. Explanations

a. Unclear in either study: sequence generation, assessment of outcomes, blindness in to outcomes data, incomplete outcomes data, and conflict of interest disclosure. In both studies allocation concealment was unclear.

b. Large confidence interval in the relative risk of intervention versus control effect in Thomsen: from 0.94 to 7.17; partially due to low number of subjects in the study (6 for each arm).

c. Large confidence interval in the ratio of means of intervention versus control effect in Thomsen: from 0.06 to 0.40 (geometric mean and SD in intervention and control groups: 0.10, 1.0 and 3.08, 12.75, respectively); partially due to low number of subjects in the study (6 for each arm).

d. CFA is considered to only indirectly reflect the immediate efficacy of treatments. Absence or clearance of CFA indicates absence of infection with adult W bancrofti. Presence of CFA indicates infection with male, fertile or non-fertile female, or dead W. bancrofti adult worms.

e. 3 persons attended a designated health facility and were kept overnight for evaluation. All persons were discharged the following day after management of the following events: abdominal pain and passing intestinal worms; fatigue, testicular swelling and scrotal pain; scrotal pain, fever, urinary incontinence, high blood pressure.

f. The four studies followed the same protocol. Variations were due to national particularities. Villages were selected based on prevalence threshold. Villages were matched and randomly allocated to arms (i.e. stratified). Open label detection bias; no blind assessment of outcomes.

g. wide confidence interval incorporating no difference to potential increased AEs (undesirable effects)

b. References

1. Thomsen, EK et al. Efficacy, Safety, and Pharmacokinetics of Coadministered Diethylcarbamazine, Albendazole, and Ivermectin for Treatment of Bancroftian Filariasis. Clin Infect Dis; 2016.

2. King CL, Suamani J Sanuku N Cheng J Satofan S Mancuso B Lombore B Siba PM Weil GJ Kazura JW. Superior Efficacy of Co-Administered Single Dose Therapy with Diethylcarbamazine, Albendazole, and Ivermectin versus Standard Therapy (Diethylcarbamazine with Albendazole) for Bancroftian Filariasis in Papua New Guinea. submitted for publication; 2017.

3. Weil GJ, et al. Death to Onchocerciasis and Lymphatic Filariasis (DOLF) Triple Drug Therapy for Lymphatic Filariasis. Community safety studies.. ongoing studies from ClinicalTrials.gov NCT02899936; 2017.

Should IDA vs. IA be used for annual mass drug administration to eliminate lymphatic filariasis in implementation units where onchocerciasis is NOT co-endemic? Bibliography:

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With ivermectin with albendazole (IA)	With ivermectin, DEC and albendazole (IDA)		Risk with ivermectin with albendazole (IA)	Risk difference with ivermectin, DEC and albendazole (IDA)
Complete microfilaria clearance (follow up: 12 months)											
81 (1 RCT) [1]	serious [1,a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	11/43 (25.6%)	29/38 (76.3%)	**RR 2.98** (1.74 to 5.12)	256 per 1,000	**507 more per 1,000** (189 more to 1,054 more)
Microfilarial density (geometric mean) (follow up: 12 months)											
81 (1 RCT) [1]	serious [1,a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	43	38	-	The mean microfilarial density (geometric mean) was **0**	Ratio of means **0.16 higher** (0.12 higher to 0.22 higher)
Inactive adult worm nest (follow up: 12 months)											
47 (1 RCT) [1]	serious [1,a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	7/27 (25.9%)	17/20 (85.0%)	**RR 3.28** (1.69 to 6.37)	259 per 1,000	**591 more per 1,000** (179 more to 1,392 more)
Circulating Filarial Antigen (CFA) prevalence (assessed with: Alere Filariasis Test Strip)											
81 (1 RCT) [1]	serious [a]	not serious	serious [c]	serious [b]	none	⨁◯◯◯ VERY LOW	43/43 (100.0%)	35/38 (92.1%)	**RR 0.92** (0.83 to 1.02)	1,000 per 1,000	**80 fewer per 1,000** (170 fewer to 20 more)
Serious adverse events (follow up: range 1 days to 7 days)											

Should IDA vs. IA be used for annual mass drug administration to eliminate lymphatic filariasis in implementation units where onchocerciasis is NOT co-endemic? Bibliography:											
Quality assessment							Summary of findings				
91 (1 RCT) [1]	serious [d]	not serious	not serious	very serious [e,f]	none	⊕◯◯◯ VERY LOW	0/49 (0.0%)	0/42 (0.0%)	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Grade 2 adverse events (follow up: range 1 days to 7 days; assessed with: subjective)											
91 (1 RCT) [1]	serious [g]	not serious	not serious	very serious [b]	none	⊕◯◯◯ VERY LOW	1/49 (2.0%)	8/42 (19.0%)	**RR 9.33** (1.22 to 71.61)	20 per 1,000	**170 more per 1,000** (4 more to 1,441 more)
Any adverse event (follow up: range 1 days to 7 days)											
91 (1 RCT) [1]	serious [g]	not serious	not serious	serious [h]	none	⊕⊕◯◯ LOW	19/49 (38.8%)	16/42 (38.1%)	**RR 0.98** (0.58 to 1.66)	388 per 1,000	**8 fewer per 1,000** (163 fewer to 256 more)

CI: Confidence interval; **RR:** Risk ratio

c. Explanations

a. unclear concealment of allocation and incomplete outcome data

b. Small event rates/small sample size

c. CFA is considered to only indirectly reflect the immediate efficacy of treatments. Absence or clearance of CFA indicates absence of infection with adult W bancrofti. Presence of CFA indicates infection with male, fertile or non-fertile female, or dead W. bancrofti adult worms.

d. Allocation concealment -- HR; Table 1 in paper shows imbalance between groups in men with worm nests (men only, women were not examined for this outcome) and circulating antigen level -- casting doubts on comparability of groups and indicating inadequate randomization.

e. Very small sample size with no events

f. Effect not estimable due to the null number of events in both groups.

g. Allocation concealment -- HR; Table 1 in paper shows imbalance between groups in men with worm nests (men only, women were not examined for this outcome) and circulating antigen level -- casting doubts on comparability of groups and indicating inadequate randomization. Open label at high risk for detection bias particularly for subjective outcomes

h. Small event rates and wide CI allowing for clinical insignificant harms, substantial harms, and even some benefit. Also estimate is fragile.

d. References

1. Bjerum CM, Aboulaye M Ouattara AF Kouadio O Marius VK Andersen B Kazura JW Weil GJ Koudou BG King CL. A randomized clinical trial comparing the effects of a single dose of ivermectin plus diethylcarbamazine plus albendazole with standard treatment of ivermectin plus albendazole for lymphatic filariasis in Côte d'Ivoire. submitted for publication; 2016.

Should biannual DA vs. annual DA be used for mass drug administration to eliminate lymphatic filariasis?
Bibliography:

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With annual DA	**With biannual DEC with albendazole (DA)**		**Risk with annual DA**	**Risk difference with biannual DEC with albendazole (DA)**
Complete microfilaria clearance (follow up: 24 months)											
153 (2 RCTs) [1,2]	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	66/76 (86.8%)	67/77 (87.0%)	**RR 0.98** (0.92 to 1.05)	868 per 1,000	**17 fewer per 1,000** (69 fewer to 43 more)
Microfilarial density (difference geometric mean) (follow up: 24 months)											
151 (2 RCTs) [1,2]	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	76	75	-	The mean microfilarial density (difference geometric mean) was **0**	Ratio of means **1.23 higher** (0.95 higher to 1.59 higher)
Inactive adult worm nests (follow up: 24 months)											
37 (1 RCT) [1]	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	14/18 (77.8%)	18/19 (94.7%)	**RR 1.15** (0.89 to 1.48)	778 per 1,000	**117 more per 1,000** (86 fewer to 373 more)
Microfilaria prevalence reduction (follow up: 36 months)											
2803 (1 observational study) [3,c,d]	serious	not serious [e]	not serious	serious [f]	none	⨁◯◯◯ VERY LOW	-/1776	-/1027 [d]	**RR 1.69** (0.53 to 5.37)	-- per --	**-- per --** (-- to --)

Should biannual DA vs. annual DA be used for mass drug administration to eliminate lymphatic filariasis? Bibliography:											
Quality assessment							**Summary of findings**				
Circulating Filarial Antigen (CFA) reduction (follow up: 36 months; assessed with: BinaxNow Filariasis ICT)											
3012 (1 observational study) [3,c]	serious	not serious [e]	not serious	not serious	none	⊕◯◯◯ VERY LOW	-/1985	-/1027	**RR 2.33** (1.12 to 4.82)	-- per --	**-- per --** (-- to --)
IgG4 reduction (follow up: 36 months; assessed with: Brugia Rapid Test)											
2803 (1 observational study) [3,c]	serious	not serious	not serious	not serious	none	⊕◯◯◯ VERY LOW	-/1776	-/1027	**RR 0.94** (0.61 to 1.44)	-- per --	**-- per --** (-- to --)

CI: Confidence interval; **RR:** Risk ratio

e. Explanations

a. All criteria in Kar 2015 had a low risk of bias, except for concealment allocation, which was unclear. In Kar 2016, selection of villages was unclear, as were unclear allocation concealment, blindness in the assessment of outcomes and blindness in relation to outcomes data.
b. small event rate/small sample size
c. There is considerable lack of information to decide on the risk of bias in each criteria. All criteria were unclear except for the funding source (low risk of bias).
d. Data refers to changes in percentage between (a) geographic areas and (b) years.
e. There is considerable variation in baseline values for this outcome.
f. wide confidence interval. Upper confidence interval is approximately five times the lower level.

f. References

1. Kar, SK et al. A clinical trial of single dose DEC and Albendazole showing reversal of lymphatic pathology in children with Wuchereria bancrofti infection in Odisha, India. PLoS Negl Trop Dis; 2017.
2. Kar, SK,et al. A randomized controlled trial of increased dose and frequency of albendazole with standard dose DEC for treatment of Wuchereria bancrofti microfilaremics in Odisha, India. PLoS Negl Trop Dis; 2015.

3. T. Supali, Y. Djuardi M. Kaisar D. Stefanie G. J. Weil and P. Fischer. Impact of once and twice yearly mass drug administration on bancroftian filariasis and soil transmitted helminth infection in central java, Indonesia. Abstract 151.. Am J Trop Med Hyg; 2015.

Should biannual ivermectin with albendazole (IA) compared to annual IA be used for mass drug administration to eliminate lymphatic filariasis in implementation units where onchocerciasis is co-endemic? Bibliography:											
Quality assessment							**Summary of findings**				

Should biannual ivermectin with albendazole (IA) compared to annual IA be used for mass drug administration to eliminate lymphatic filariasis in implementation units where onchocerciasis is co-endemic?
Bibliography:

Quality assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With annual albendazole with Ivermectin	**With biannual Albendazole with Ivermectin**		**Risk with annual albendazole with Ivermectin**	**Risk difference with biannual Albendazole with Ivermectin**
Microfilaria prevalence (follow up: 24 months)											
36 (1 RCT) [1]	serious [a]	not serious	not serious	very serious [b]	none	⨁◯◯◯ VERY LOW	15/18 (83.3%)	13/18 (72.2%)	**RR 0.87** (0.61 to 1.23)	833 per 1,000	**108 fewer per 1,000** (325 fewer to 192 more)
Microfilaraemia prevalance reduction (follow up: 24 months)											
11739 (2 observational studies) [2,3,c]	very serious [d]	not serious	not serious	serious [e]	none	⨁◯◯◯ VERY LOW	-/6064	-/5675	**RR 0.83** (0.54 to 1.28)	-- per --	**-- per --** (-- to --)
Circulating Filarial Antigen (CFA) reduction (follow up: 24 months; assessed with: BinaxNow Filariasis ICT / Alere Filariasis Test Strip)											
11739 (2 observational studies) [2,3,c]	very serious [d]	not serious	serious [g]	serious [e]	none	⨁◯◯◯ VERY LOW	-/6064	-/5675	**RR 0.55** (0.17 to 1.82)	-- per --	**-- per --** (-- to --)

CI: Confidence interval; **RR:** Risk ratio

g. Explanations

a. High risk of bias due to lack of allocation concealment, blindness in the assessment of outcomes and data. Rest of the criteria are low risk of bias.
b. small sample size and wide confidence intervals
c. Both studies are non-randomised trials with controls
d. Sampling was unclear in one study (CIV) and was not really randomised in the other one (Liberia). High risk of bias due to lack (Liberia) or unclear (CIV) sequence allocation and no allocation concealment. Rest of ROB criteria were unclear. Source of funding: low risk of bias.
e. wide confidence interval

g. CFA is considered to only indirectly reflect the efficacy of treatments. Absence or clearance of CFA indicates absence of infection with adult W bancrofti. Presence of CFA indicates infection with male, fertile or non-fertile female, or dead W. bancrofti adult worms.

h. References

1. Tafatatha, TT et al. Randomised controlled clinical trial of increased dose and frequency of albendazole and ivermectin on Wuchereria bancrofti microfilarial clearance in northern Malawi. Trans R Soc Trop Med Hyg; 2015.

2. Bolay FK, Fischer PU,Weil GJ.. Mass Drug Administration for Lymphatic Filariasis and Onchocerciasis for Liberia (DOLF-LIBERIA).. ongoing study from Clinical Trials.gov NCT01905436; 2017.

3. Meite A, Weil GJ,Fischer PU.. Optimization of Mass Drug Administration With Existing Drug Regimens for Lymphatic Filariasis and Onchocerciasis for Ivory Coast (DOLF-Ivory Coast). ongoing study from Clinicaltrials.gov NCT02032043; 2017.

Should biannual ALB vs. annual ALB be used for mass drug administration to eliminate lymphatic filariasis in implementation units where loiasis is co-endemic?
Bibliography:

Quality assessment							Summary of findings			
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Impact**	
							With annual albendazole	**With biannual albendazole**		
Microfilaria prevalence reduction (follow up: 36 months)										
1428 (1 observational study) [1]	serious [a]	not serious	serious [b]	serious [c]	none	⊕◯◯◯ VERY LOW	Post-treatment with biannual albandazole there was 94.3% reduction in MF prevalence (Pion et al. 2017). This was a single-arm community cohort study. We indirectly compared this with Ismail et al. 1998. After 15 months 1/12 patient (<10%) was cleared of MF with 600 mg of albendazole. [2]			
Circulating Filarial Antigen reduction (CFA) (follow up: 36 months; assessed with: BinaxNow Filariasis ICT)										
1434 (1 observational study) [1]	serious [a]	not serious	serious [b,d]	serious [c]	none	⊕◯◯◯ VERY LOW	Post-treatment with biannual albandazole there was 72.8% reduction in CFA prevalence (Pion et al. 2017). This was a single-arm community cohort study. We indirectly compared this with Ismail et al. 1998. After 15 months 0/12 patient was cleared of antigen with 600 mg of albendazole. [2]			

CI: Confidence interval; **RR:** Risk ratio

i. Explanations

a. This is a single arm study. No clear criteria for the selection of participants although the study seems to imply that all inhabitants in the study are were eligible.
b. indirect comparison
c. for the indirect comparison study, there was small sample size N=12
d. CFA is considered to only indirectly reflect the efficacy of treatments. Absence or clearance of CFA indicates absence of infection with adult W bancrofti. Presence of CFA indicates infection with male, fertile or non-fertile female, or dead W. bancrofti adult worms.

j. References

1. Pion, SD et al. Effect of 3 years of biannual mass drug administration with albendazole on lymphatic filariasis and soil-transmitted helminth infections: a community-based study in Republic of the Congo. Lancet Infect Dis; 2017.
2. Ismail, M.M.,et al. Efficacy of single dose combinations of albendazole, ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis. Trans R Soc Trop Med Hyg; 1998.

Annex 8. CASP quality assessments (feasibility scoping review)

Table 14 Adapted CASP quality assessment tool for qualitative studies checklist evaluation of included studies

	1	2	3	4	5	6	7	8	Overall assessment
Amarillo 2008 (13)	No	No	Yes	Yes	Unclear	No	Unclear		Moderate to severe concerns - poor reporting of the qualitative methodology and findings
Babu 2004 (14)	No	No	Yes	Yes	Yes	No	No	Analysis looked at frequency of themes	Moderate to severe concerns - poor reporting of the qualitative methodology and findings
Babu 2004 (15)	Unclear	No	Yes	Yes	Yes	No	No	Analysis makes separation of quantitative and qualitative data more difficult	Moderate to severe concerns - poor reporting of the qualitative methodology and findings
Babu 2010 (16)	Unclear	No	Yes	Yes	Yes	No	No		Moderate to severe concerns - poor reporting of the qualitative methodology and findings
Baker 2007 (17)	Yes	No	Yes	Yes	Yes	No	Yes	Write up makes separation of quantitative and qualitative data more difficult	Moderate to severe concerns - poor reporting of the qualitative methodology and findings
da-Costa Vroom 2015 (18)	Yes	Yes	Yes	Yes	Yes	No	Yes		Minor concerns
Hussain 2014 (19)	Yes	No	Yes	Yes	Yes	Some	Yes		Minor to moderate concerns - poor reporting of sampling
King 2011 (20)	Yes	Unclear	Yes	Yes	Yes	No	No		Moderate concerns - lack of discussion of reflexivity and ethical considerations and unclear sampling
Kisoka 2016 (21)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes		Minor concerns
Kisoka 2016 (22)	Yes	No	Yes	Yes	Yes	No	Yes		Minor to moderate concerns - poor reporting of sampling and lack of discussion of reflexivity
Krentel 2012 (23)	Yes	Yes	Yes	Yes	Yes	No	Yes		Minor Concerns
Njomo 2012 (24)	Yes	No	Yes	Yes	Yes	No	Yes		Minor to moderate concerns - poor reporting of sampling and lack of discussion of reflexivity
Njomo 2014 (25)	Yes	Yes	Yes	Yes	Yes	No	Yes		Minor concerns
Wynd 2007 (26)	Yes	Unclear	Yes	Unclear	Yes	No	Yes		Moderate concerns - poor reporting of sampling and analysis and lack of discussion of reflexivity

1. Are the setting/s and context described adequately?; 2 Is the sampling strategy described and is this appropriate?; 3. Is the data collection strategy described and justified?; 4. Is the data analysis described and is this appropriate?; 5. Are the claims made/findings supported by sufficient evidence?; 6. Is there evidence of reflexivity?; 7. Does the study demonstrate sensitivity to ethical concerns?: 8 Any other concerns.

Annex 9. List of included studies in the qualitative scoping review.

SR01. Amarillo MLE, Belizario VY, Sadiang-Abay JT, Sison SAM, Dayag AMS. Factors associated with the acceptance of mass drug administration for the elimination of lymphatic filariasis in Agusan del Sur, Philippines. Parasites and Vectors. 2008;1(1).

SR02. Babu BV, Nath N. The programme to eliminate lymphatic filariasis in Orissa, India: The attitudes of some programme partners. Annals of Tropical Medicine and Parasitology. 2004;98(7):751-6.

SR03. Babu BV, Kar SK. Coverage, compliance and some operational issues of mass drug administration during the programme to eliminate lymphatic filariasis in Orissa, India. Tropical Medicine and International Health. 2004;9(6):702-9.

SR04. Babu BV. A qualitative study on the adverse reactions of mass treatment for lymphatic filariasis in Orissa, India. Asian Pacific Journal of Tropical Medicine. 2010;3(1):55-8.

SR05. Baker MC, McFarland DA, Gonzales M, Diaz MJ, Molyneux DH. The impact of integrating the elimination programme for lymphatic filariasis into primary health care in the Dominican Republic. International Journal of Health Planning and Management. 2007;22(4):337-52.

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