Annex 1. GRADE Table 1: annual IDA versus annual DA

Question: Should IDA versus DA be used for annual MDA to eliminate lymphatic filariasis in implementation units where onchocerciasis is NOT co-endemic?
Setting: Lymphatic filariasis endemic communities (either *Wuchereria bancrofti* or *Brugia* spp.) in countries using DA for the elimination of lymphatic filariasis

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Annual IDA**	**Annual DA**	**Relative (95% CI)**	**Absolute (95% CI)**		
Complete mf clearance (assessed with: membrane filtration of 2 ml blood) (follow up: 24 months)												
2[1,2]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	58/60 (96.7%)	33/61 (54.1%)	**RR 1.75** (1.39 to 2.20)	**406 more per 1000** (from 211 more to 649 more)	⊕⊕◯◯ LOW	CRITICAL
Microfilarial density (geometric mean) (follow up: 24 months)												
2[1,2]	randomized trials	serious[a]	not serious	not serious	serious[c]	none	64	64	–	Ratio of means **0.1 higher** (0.07 higher to 0.14 higher)	⊕⊕◯◯ LOW	IMPORTANT
CFA (assessed with: Alere Filariasis Test Strip)												
1[2]	randomized trials	serious[a]	not serious	serious[d]	not serious	none	57/58 (98.3%)	57/58 (98.3%)	**RR 1.00** (0.95 to 1.04)	**0 fewer per 1000** (from 49 fewer to 39 more)	⊕⊕◯◯ LOW	IMPORTANT
SAEs (assessed with: cohort event monitoring)												
4[3]	randomized trials	serious[d]	not serious	not serious	not serious	none	0/10486 (0.0%)	3/10329 (0.0%)[e]	**RR 0.48** (0.08 to 2.90)	**15 fewer per 100 000** (from 27 fewer to 55 more)	⊕⊕⊕◯ MODERATE	CRITICAL
AEs Grade 3 and 4 (assessed with: cohort event monitoring)												
4[3]	randomized trials	serious[d]	not serious	not serious	not serious	none	7/10486 (0.1%)	12/10329 (0.1%)	**RR 0.57** (0.22 to 1.45)	**50 fewer per 100 000** (from 91 fewer to 52 more)	⊕⊕⊕◯ MODERATE	CRITICAL
AEs Grade 2 to 4 in communities with no prior MDA												

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Annual IDA	Annual DA	Relative (95% CI)	Absolute (95% CI)		
2[3]	randomized trials	serious[d]	not serious	not serious	not serious	none	50/3430 (1.5%)	33/3180 (1.0%)	**RR 1.51** (0.96 to 2.39)	**5 more per 1000** (from 0 fewer to 14 more)	⊕⊕⊕◯ MODERATE	CRITICAL
AEs Grade 2 to 4 among mf positive persons (assessed with: cohort event monitoring)												
4[3]	randomized trials	serious[d]	not serious	not serious	serious[f]	none	29/447 (6.5%)	6/414 (1.4%)	**RR 3.47** (0.68 to 17.73)	**36 more per 1000** (from 5 fewer to 242 more)	⊕⊕◯◯ LOW	IMPORTANT
Any AEs among mf positive persons (assessed with: cohort event monitoring)												
4[3]	randomized trials	serious[d]	not serious	not serious	serious[f]	none	181/447 (40.5%)	99/414 (23.9%)	**RR 1.50** (0.99 to 2.27)	**120 more per 1000** (from 2 fewer to 304 more)	⊕⊕◯◯ LOW	IMPORTANT
AEs Grade 2 (assessed with: cohort event monitoring)												
4[3]	randomized trials	serious[d]	serious	not serious	not serious	none	99/10486 (0.9%)	82/3005 (2.7%)	**RR 1.27** (0.26 to 6.19)	**7 more per 1000** (from 20 fewer to 142 more)	⊕⊕◯◯ LOW	IMPORTANT
Any AEs (assessed with: cohort event monitoring)												
4[3]	randomized trials	serious[d]	serious	not serious	not serious	none	1100/10519 (10.5%)	1138/10677 (10.7%)	**RR 1.10** (0.67 to 1.78)	**11 more per 1000** (from 35 fewer to 83 more)	⊕⊕◯◯ LOW	NOT IMPORTANT

AE, adverse event; CFA, circulating filarial antigen; CI, confidence interval; DA, diethylcarbamazine + albendazole; IDA, ivermectin + diethylcarbamazine + albendazole; mf, microfilaraemia; RR, relative risk; SAE, serious adverse event

[a] Unclear in either study: sequence generation, assessment of outcomes, blindness in relation to outcomes data, incomplete outcomes data, and conflict of interest disclosure. In both studies allocation concealment was unclear.
[b] Large CI 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 CI in the ratio of means of intervention versus control effect in Thomsen: from 0.06 to 0.40 (geometric mean and standard deviation 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] 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.
[e] Three persons who attended a designated health facility and were kept overnight for evaluation were all 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] Wide confidence interval incorporating no difference to potential increased AEs (undesirable effects).
[1] Thomsen EK, Sanuku N, Baea M, Satofan S, Maki E, Lombore B et al. Efficacy, safety, and pharmacokinetics of coadministered diethylcarbamazine, albendazole, and ivermectin for treatment of bancroftian filariasis. Clin Infect Dis. 2016;62:334–41.
[2] King CL, Suamani J, Sanuku N, Cheng J, Satofan S, Mancuso B et al. 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 [under review]; 2017.
[3] Weil GJ, King CL. Death to onchocerciasis and lymphatic filariasis (DOLF) triple drug therapy for lymphatic filariasis. Community safety studies. 2016 (ClinicalTrials.gov identifier NCT02899936). Includes:
Jambulingam P. Krishnamoorthy K, Death to onchocerciasis and lymphatic filariasis (DOLF) triple drug therapy for lymphatic filariasis. Community safety studies in India; 2016.
Lemoine JF, Dubray C. Death to onchocerciasis and lymphatic filariasis (DOLF) triple drug therapy for lymphatic filariasis. Community safety studies in Haiti; 2016.
Siba P, Robinson L. Death to onchocerciasis and lymphatic filariasis (DOLF) triple drug therapy for lymphatic filariasis. Community safety studies in Papua New Guinea; 2016.
Supali T, Djuardi Y. Death to onchocerciasis and lymphatic filariasis (DOLF) triple drug therapy for lymphatic filariasis. Community safety studies in Indonesia; 2016.

Annex 1. GRADE Table 2: biannual DA versus annual DA

Question: Should biannual DA versus annual DA be used for MDA to eliminate lymphatic filariasis in implementation units where onchocerciasis is NOT co-endemic?
Setting: Lymphatic filariasis endemic communities (either *Wuchereria bancrofti* or *Brugia* spp.) in countries using DA for the elimination of lymphatic filariasis

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Biannual DA**	**Annual DA**	**Relative (95% CI)**	**Absolute (95% CI)**		
Complete mf clearance (follow up: 24 months; assessed with: membrane filtration of 1 ml blood)												
2[1,2]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	67/77 (87.0%)	66/76 (86.8%)	**RR 0.98** (0.92 to 1.05)	**17 fewer per 1000** (from 69 fewer to 43 more)	⨁⨁◯◯ LOW	CRITICAL
Microfilarial density (difference geometric mean) (follow up: 24 months)												
2[1,2]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	75	76	–	Ratio of means **1.23 higher** (0.95 higher to 1.59 higher)	⨁⨁◯◯ LOW	IMPORTANT
Inactive adult worm nests (follow up: 24 months)												
1[1]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	18/19 (94.7%)	14/18 (77.8%)	**RR 1.15** (0.89 to 1.48)	**117 more per 1000** (from 86 fewer to 373 more)	⨁⨁◯◯ LOW	IMPORTANT
Mf prevalence reduction (follow up: 36 months; assessed with: membrane filtration of 1 ml blood)												
1[3]	observational studies[c]	serious	not serious[d]	not serious	serious[e]	none	−/1027[f]	−/1776[f]	**RR 1.69** (0.53 to 5.37)	**-- per --** (from -- to --)[g]	⨁◯◯◯ VERY LOW	IMPORTANT
CFA reduction (follow up: 36 months; assessed with: BinaxNow Filariasis ICT)												
1[3]	observational studies[c]	serious	not serious[d]	not serious	not serious	none	−/1027[f]	−/1985[f]	**RR 2.33** (1.12 to 4.82)	**-- per --** (from -- to --)[g]	⨁◯◯◯ VERY LOW	IMPORTANT
IgG4 reduction (follow up: 36 months; assessed with: Brugia Rapid Test)												
1[3]	observational studies[c]	serious	not serious	not serious	not serious	none	−/1027[f]	−/1776[f]	**RR 0.94** (0.61 to 1.44)	**-- per --** (from -- to --)[g]	⨁◯◯◯ VERY LOW	IMPORTANT

CFA, circulating filarial antigen; CI, confidence interval; DA, diethylcarbamazine + albendazole; mf, microfilaraemia; RR, relative risk

[a] All criteria in Kar et al (2015) had a low risk of bias, except for concealment allocation, which was unclear. In Kar et al (2017), there was allocation concealment, blindness in the assessment of outcomes and blindness in relation to outcomes data.
[b] Small event rate or 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] There is considerable variation in baseline values for this outcome.
[e] Wide CI. The upper CI is approximately five times the lower level.
[f] Data refer to changes in percentage between (i) geographical areas and (ii) years; only the total number of persons evaluated in each community is listed.
[g] Absolute is not applicable for the outcome. The outcome of interest is reduction in prevalence at follow-up relative to baseline prevalence taking into account variation in baseline prevalence between control and intervention.

[1] Kar SK, Dwibedi B, Das BK, Agrawala BK, Ramachandran CP, Horton J. Lymphatic pathology in symptomatic children with *Wuchereria bancrofti* infection in children in Odisha, India and its reversal with DEC and albendazole. PLoS Negl Trop Dis. 2017;11: e0005631. https://doi.org/10.1371/journal.pntd.0005631.

[2] Kar SK, Dwibedi B, Kerketa AS, Maharana A, Panda SS, Chandra Mohanty P 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:e0003583.

[3] Supali T, Djuardi Y, Kaisar M, Stefanie D, Weil GJ, Fischer P. Impact of once and twice yearly mass drug administration on bancroftian filariasis and soil transmitted helminth infection in central java, Indonesia. Am J Trop Med Hyg. 2015;93(4 Supplement, Abstract 151 (Clinicaltrials.gov identifier NCT01905423)).

Annex 1. GRADE Table 3: annual IDA versus annual IA

Question: Should IDA versus IA be used for annual MDA to eliminate lymphatic filariasis in implementation units where onchocerciasis is NOT co-endemic?
Setting: Lymphatic filariasis endemic communities (*Wuchereria bancrofti*) in countries co-endemic with onchocerciasis using IA for the elimination of lymphatic filariasis

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Annual IDA**	**Annual IA**	**Relative (95% CI)**	**Absolute (95% CI)**		
Complete mf clearance (follow up: 12 months; assessed with: membrane filtration of 2 ml blood)												
1[1]	randomized trials	serious[1,a]	not serious	not serious	serious[b]	none	29/38 (76.3%)	11/43 (25.6%)	**RR 2.98** (1.74 to 5.12)	**507 more per 1000** (from 189 more to 1000 more)	⨁⨁◯◯ LOW	CRITICAL
Microfilarial density (geometric mean) (follow up: 12 months)												
1[1]	randomized trials	serious[1,a]	not serious	not serious	serious[b]	none	38	43	–	Ratio of means **0.16 higher** (0.12 higher to 0.22 higher)	⨁⨁◯◯ LOW	IMPORTANT
Inactive adult worm nest (follow up: 12 months)												
1[1]	randomized trials	serious[1,a]	not serious	not serious	serious[b]	none	17/20 (85.0%)	7/27 (25.9%)	**RR 3.28** (1.69 to 6.37)	**591 more per 1000** (from 179 more to 1000 more)	⨁⨁◯◯ LOW	IMPORTANT
CFA (assessed with: Alere Filariasis Test Strip)												
1[1]	randomized trials	serious[a]	not serious	serious[c]	serious[b]	none	35/38 (92.1%)	43/43 (100.0%)	**RR 0.92** (0.83 to 1.02)	**80 fewer per 1000** (from 170 fewer to 20 more)	⨁◯◯◯ VERY LOW	IMPORTANT
SAEs among mf positive persons (follow up: range 1 day to 7 days)												

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Annual IDA	Annual IA	Relative (95% CI)	Absolute (95% CI)		
1[1]	randomized trials	serious[d]	not serious	not serious	very serious[e,f]	none	0/42 (0.0%)	0/49 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
AEs Grade 2 among mf positive persons (follow up: range 1 day to 7 days; assessed with: subjective)												
1[1]	randomized trials	serious[g]	not serious	not serious	very serious[b]	none	8/42 (19.0%)	1/49 (2.0%)	**RR 9.33** (1.22 to 71.61)	**170 more per 1000** (from 4 more to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Any AE among mf positive persons (follow up: range 1 day to 7 days)												
1[1]	randomized trials	serious[g]	not serious	not serious	serious[h]	none	16/42 (38.1%)	19/49 (38.8%)	**RR 0.98** (0.58 to 1.66)	**8 fewer per 1000** (from 163 fewer to 256 more)	⨁⨁◯◯ LOW	NOT IMPORTANT

AE, adverse event; CFA, circulating filarial antigen; CI, confidence interval; IA, ivermectin + albendazole; IDA, ivermectin + diethylcarbamazine + albendazole; MDA, mass drug administration; mf, microfilaraemia; RR, relative risk; SAE, serious adverse event

[a] Unclear concealment of allocation and incomplete outcome data
[b] Small event rates or 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 clinically insignificant harms, substantial harms and even some benefit. Also estimate is fragile.

[1] Bjerum CM, Aboulaye M, Ouattara AF, Kouadio O, Marius VK, Andersen B et al. 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 [under review]; 2017.

Annex 1. GRADE Table 4: biannual IA versus annual IA

Question: Should biannual IA versus annual IA be used for MDA to eliminate lymphatic filariasis in implementation units where onchocerciasis is co-endemic?
Setting: Lymphatic filariasis endemic communities (*Wuchereria bancrofti*) in countries co-endemic with onchocerciasis using IA for the elimination of lymphatic filariasis

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biannual IA	Annual IA	Relative (95% CI)	Absolute (95% CI)		
Mf prevalence (follow up: 24 months; assessed with: membrane filtration of 1 ml blood)												
1[1]	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	13/18 (72.2%)	15/18 (83.3%)	**RR 0.87** (0.61 to 1.23)	**108 fewer per 1000** (325 fewer to 192 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Mf prevalence reduction (follow up: 24 months; assessed with: night blood smear using 60 µl of blood)												
2[2,3]	observational studies[c]	very serious[d]	not serious	not serious	serious[e]	none	−/5675[h]	−/6064[h]	**RR 0.83** (0.54 to 1.28)	**-- per --** (from -- to --)[f]	⊕◯◯◯ VERY LOW	IMPORTANT
CFA reduction (follow up: 24 months; assessed with: BinaxNow Filariasis ICT / Alere Filariasis Test Strip)												
2[2,3]	observational studies[c]	very serious[d]	not serious	serious[g]	serious[e]	none	−/5675[h]	−/6064[h]	**RR 0.55** (0.17 to 1.82)	**-- per --** (from -- to --)[f]	⊕◯◯◯ VERY LOW	IMPORTANT

AE, adverse event; CFA, circulating filarial antigen; CI, confidence interval; DA, diethylcarbamazine combined with albendazole; ICT, immunochromatographic test; IDA, ivermectin combined with diethylcarbamazine and albendazole; mf, microfilaraemia; RR, relative risk; SAE, serious adverse event

[a] High risk of bias due to lack of allocation concealment, and blindness in the assessment of outcomes and data. Rest of the criteria are low risk of bias.
[b] Small sample size and wide CIs.
[c] Both studies are non-randomized trials with controls.
[d] Sampling was unclear in one study[3] and randomization was unclear in the other study.[2] High risk of bias due to lack[2] or unclear[3] sequence allocation and no allocation concealment. Rest of risk of bias criteria were unclear. Source of funding: low risk of bias.
[e] Wide CI.
[f] Absolute is not applicable for the outcome. The outcome of interest is reduction in prevalence at follow-up relative to baseline prevalence taking into account variation in baseline prevalence between control and intervention.
[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] Data refer to changes in percentage between (1) geographical areas and (ii) years; only the total number of persons evaluated in each community is listed.

[1] Tafatatha TT, Ngwira BM, Taegtmeyer M, Phiri AJ, Wilson TP, Banda LG 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;109:393–9.
[2] Bolay FK, Fischer PU, Weil GJ. Mass drug administration for lymphatic filariasis and onchocerciasis for Liberia (DOLF-LIBERIA). 2013, Clinical Trials.gov identifier NCT01905436.
[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). 2014, Clinicaltrials.gov NCT02032043.

Annex 1. GRADE Table 5: biannual ALB versus annual ALB

Question: Should biannual ALB versus annual ALB be used for MDA to eliminate lymphatic filariasis in implementation units where loiasis is co-endemic?
Setting: Lymphatic filariasis endemic communities (*Wuchereria bancrofti*) co-endemic with loiasis where ivermectin has not already been distributed

Quality assessment							Impact	Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Mf prevalence reduction (follow up: 36 months; assessed with: two night blood smears using 70 µl of blood)									
1[1]	observational studies	serious[a]	not serious	serious[b]	serious[c]	none	Post-treatment with biannual albandazole, mf prevalence was reduced by 94.3%.[1] This was a single-arm community cohort study. We indirectly compared this with Ismail et al (1998).[2] After 15 months 1/12 patients (< 10%) was cleared of mf with albendazole (600 mg).[2]	⊕◯◯◯ VERY LOW	IMPORTANT
CFA reduction (follow up: 36 months; assessed with: BinaxNow Filariasis ICT)									
1[1]	observational studies	serious[a]	not serious	serious[b,d]	serious[c]	none	Post-treatment with biannual albandazole, CFA prevalence was reduced by 72.8%.[1] This was a single-arm community cohort study. We indirectly compared this with Ismail et al (1998).[2] After 15 months 0/12 patients was cleared of antigen with albendazole (600 mg).[2]	⊕◯◯◯ VERY LOW	IMPORTANT

ALB, albendazole; CFA, circulating filarial antigen; ICT, immunochromatographic test; MDA, mass drug administration; mf, microfilaraemia
[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 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.

[1] Pion SDS, Chesnais CB, Weil GJ, Fischer PU, Missamou F, Boussinesq M. 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;17:763–9.
[2] Ismail MM, Jayakody RL, Weil GJ, Nirmalan N, Jayasinghe KS, Abeyewickrema W 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;92:94–7.