INFECTIOUS DISEASES DATA OBSERVATORY

Optimal choice of long-acting antimalarial regimens for seasonal malaria chemoprevention: Systematic review and Network Meta-analysis

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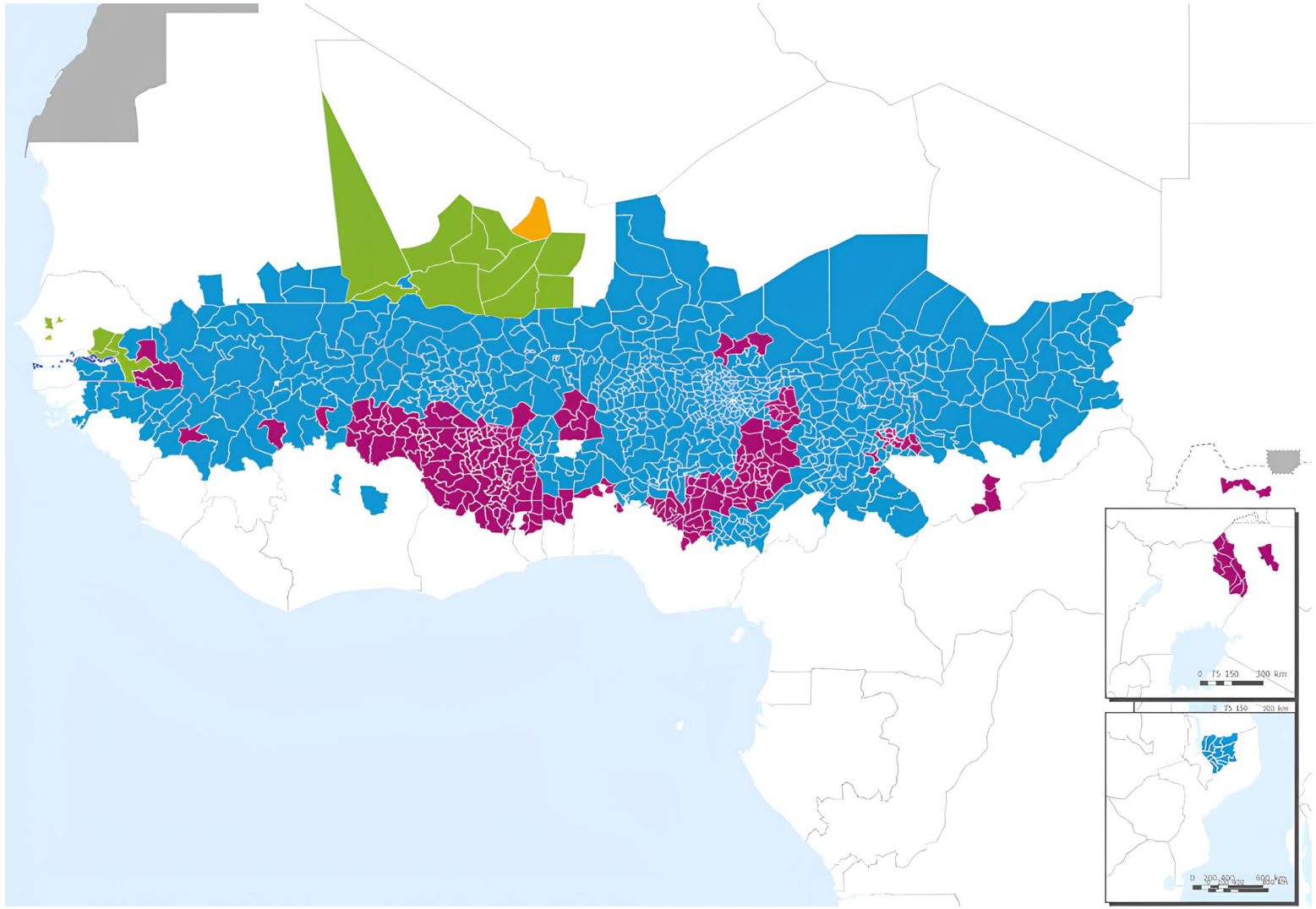
Seasonal Malaria Chemoprevention

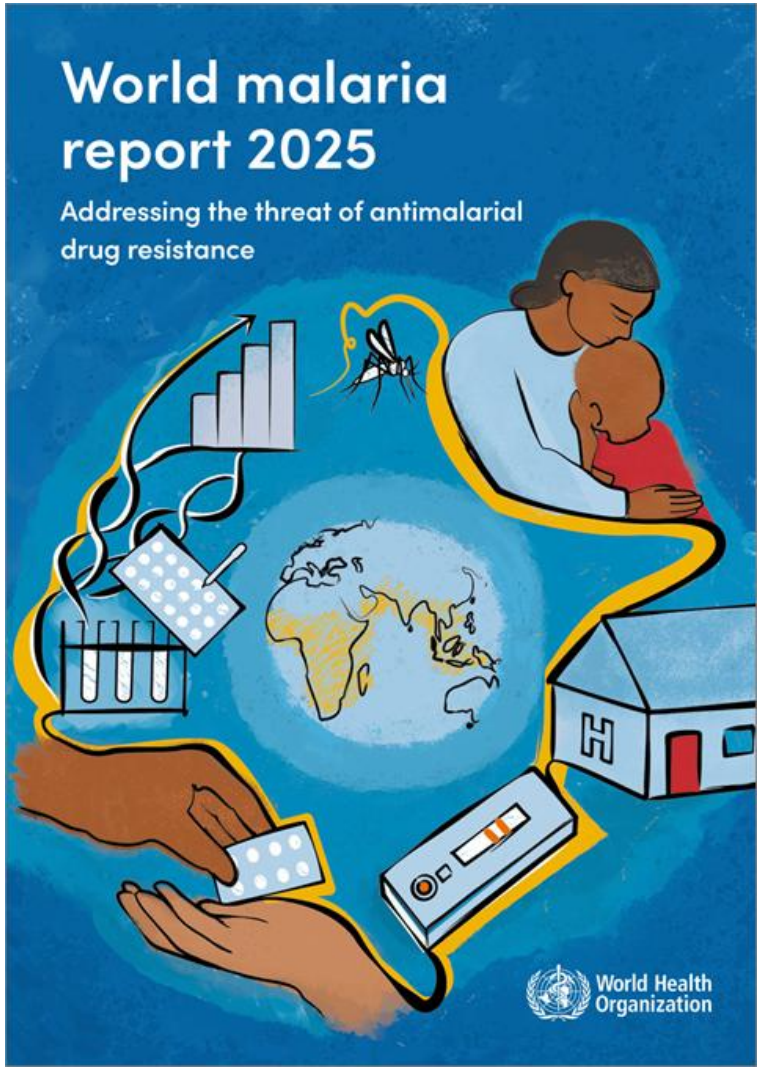
SMC = Intermittent administration of antimalarials during the malaria **'season'**, regardless of baseline infection status

- **Initial deployment -** under-five children in Sahelian West Africa
- **Current WHO policy -** flexible deployment across Sub-Saharan Africa (SSA) + expanded age eligibility (up to 10 years)

Seasonal Malaria Chemoprevention

2024: ~ 54 million children (3m-10years) received SMC across 19 countries





Some gaps on SMC deployment

- Treatment effect heterogeneity in protective efficacy
- **Optimal antimalarial regimen(s) for SMC**
- Pharmacometric methods to evaluate efficacy and monitor for resistance

Current regimen

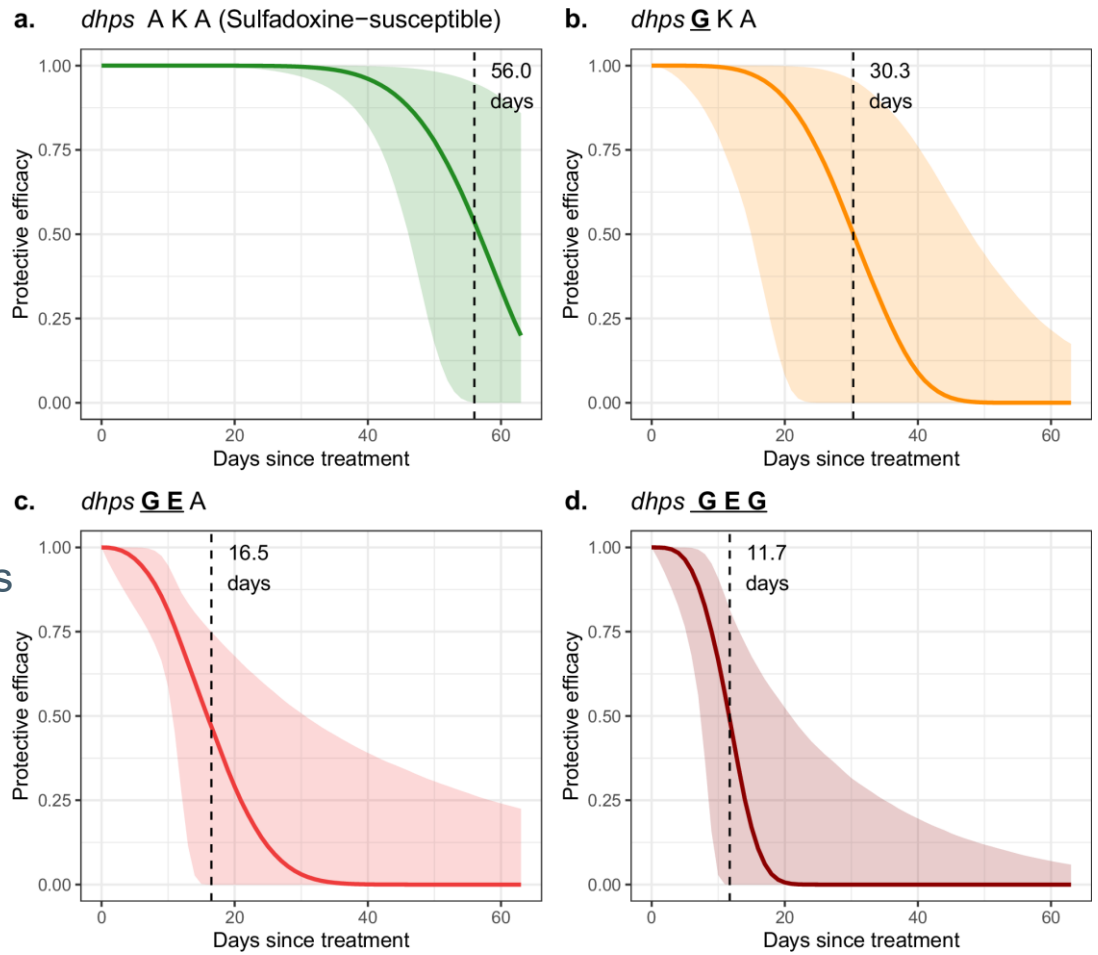
Sulphadoxine-Pyrimethamine + Amodiaquine (SPAQ)

Age	SP	AQ
3-12m	250/12.5mg (1/2 tab)	75mg * 3 (1/2 tab)
12-59m	500/25mg (1 tab)	150mg * 3 (1 tab)
>60m	25/1.25mg/kg (2 tabs)	10mg/kg (2 tabs * 3)

Pharmacology of long-acting antimalarials used in chemoprevention

Sulphadoxine-pyrimethamine

- Antifolate pathway drugs
- T1/2 : **S ~ 8 days + P ~ 4 days**
- Action: Blood-stage asexual parasites. Synergistic effect
- Post-treatment protective efficacy **compromised** by serial mutations in ***pfdhs*** and ***pfdhr*** genes



Mousa, A., Cuomo-Dannenburg, G., Thompson, H.A. *et al.* Impact of *dhps* mutations on sulfadoxine-pyrimethamine protective efficacy and implications for malaria chemoprevention. *Nat Commun* **16**, 4268 (2025). https://doi.org/10.1038/s41467-025-58326-z

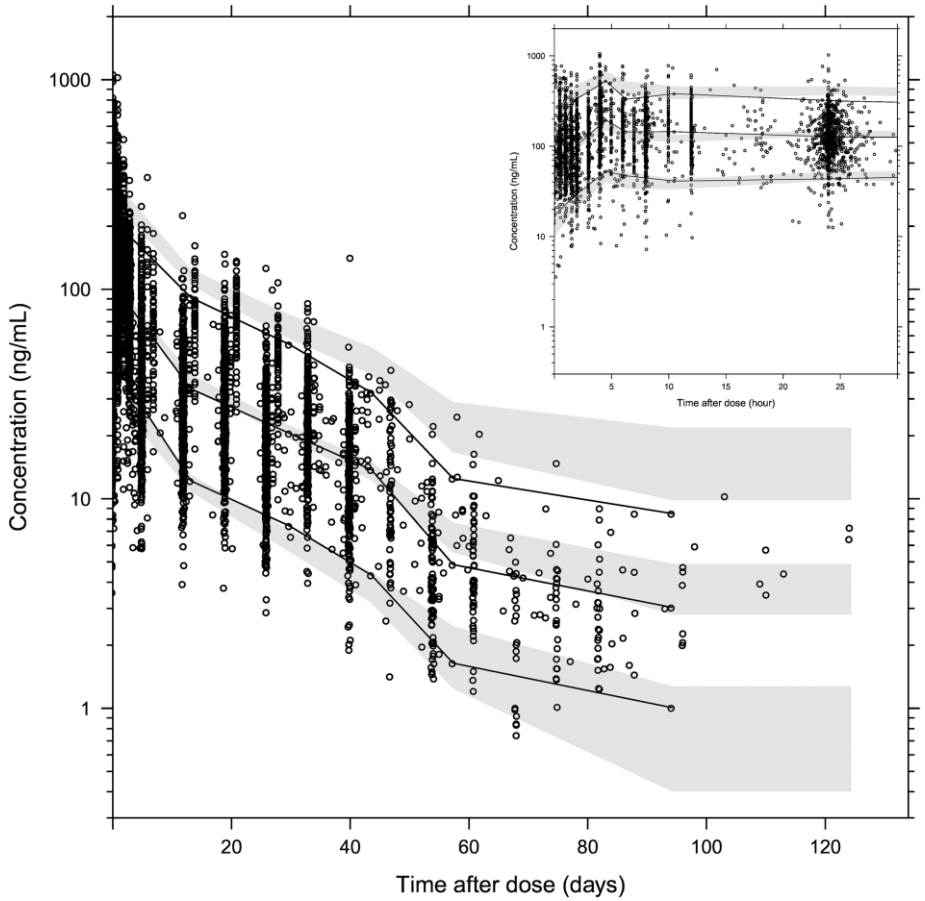
Amodiaquine

- 4-aminoquinolone
- T1/2: AQ: 15h, DEAQ ~ 12 days
- Post treatment protection ~ 10-18 days
- Compromised by **pfcrt 76T pfmdr1 86Y** and **adherence**

Pharmacology of long-acting antimalarials used in chemoprevention

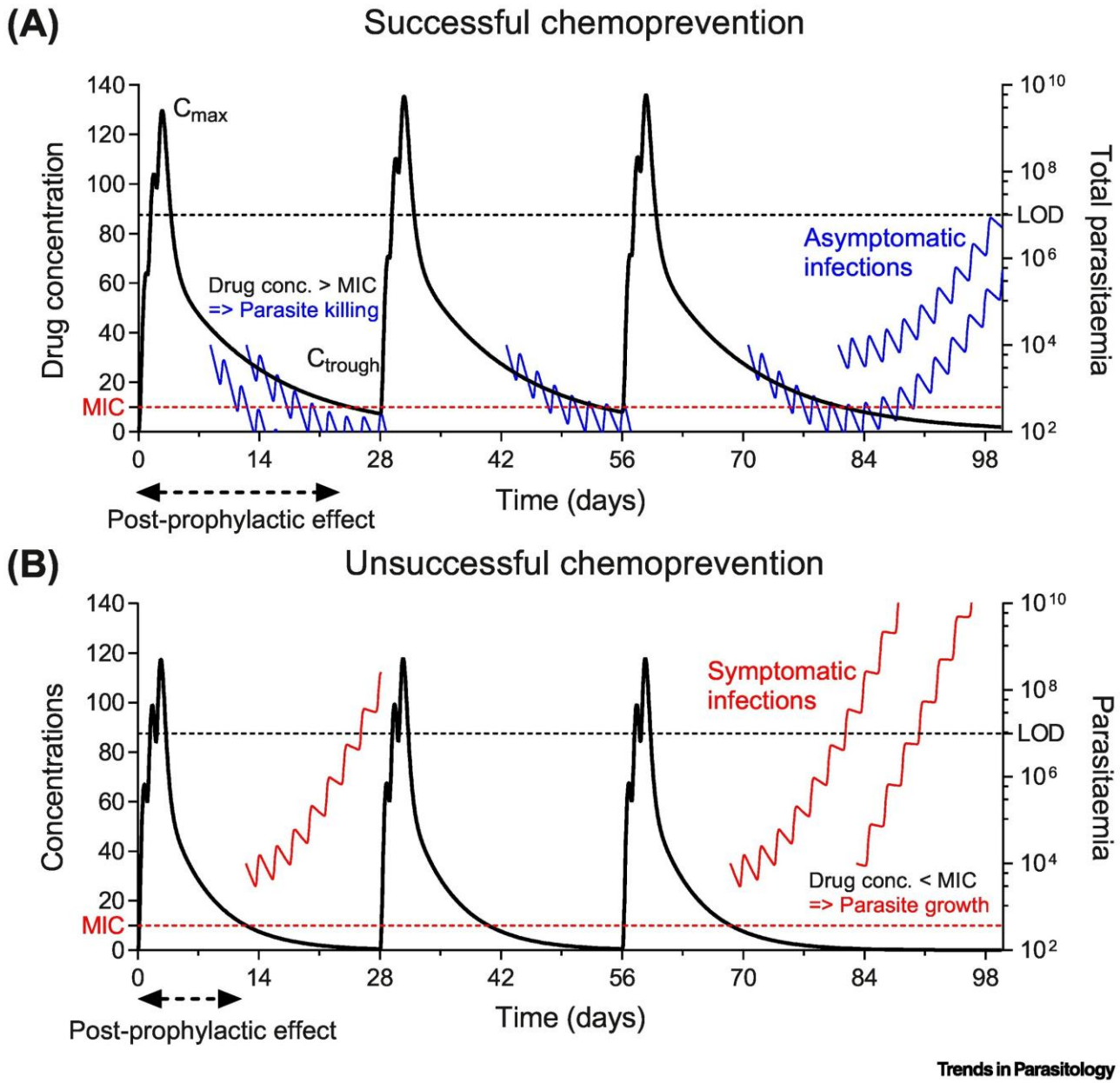
Piperaquine

- T1/2: 20-30 days
- Multiphasic elimination profile



Population Pharmacokinetic Properties of Piperaquine in Falciparum Malaria: An Individual Participant Data Meta-Analysis Hoglund RM, Workman L, Edstein MD, Thanh NX, Quang NN, et al. (2017) Population Pharmacokinetic Properties of Piperaquine in Falciparum Malaria: An Individual Participant Data Meta-Analysis. PLOS Medicine 14(1): e1002212. https://doi.org/10.1371/journal.pmed.1002212

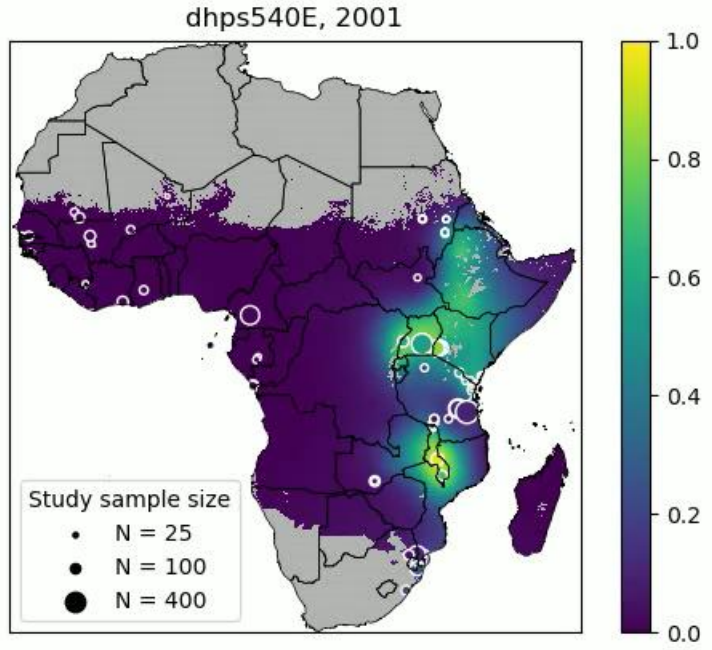
Why long-acting drugs? Successful chemoprevention



Alternative regimens for SMC

SP: Resistance

- Mutations in *pfdhs* reduce post-treatment prophylactic effect
- High prevalence of pfdhpsK540E mutant in E/S Africa



AQ: Overlapping treatment and chemoprevention

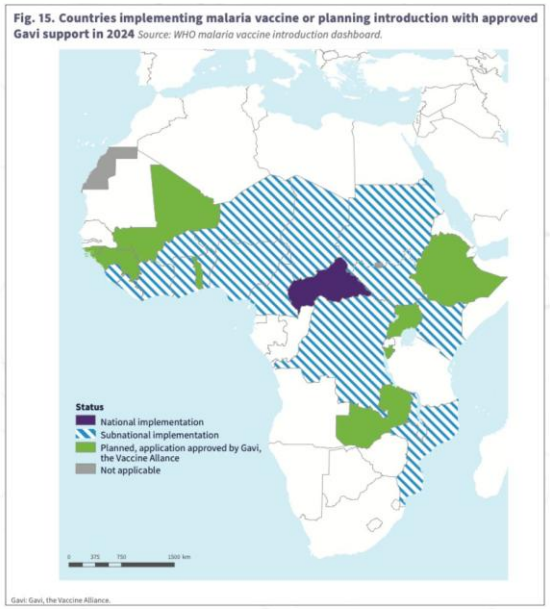
- AS-AQ (ACT) and AL + AQ (TACT)

AQ: Adherence

- Gastrointestinal side effects

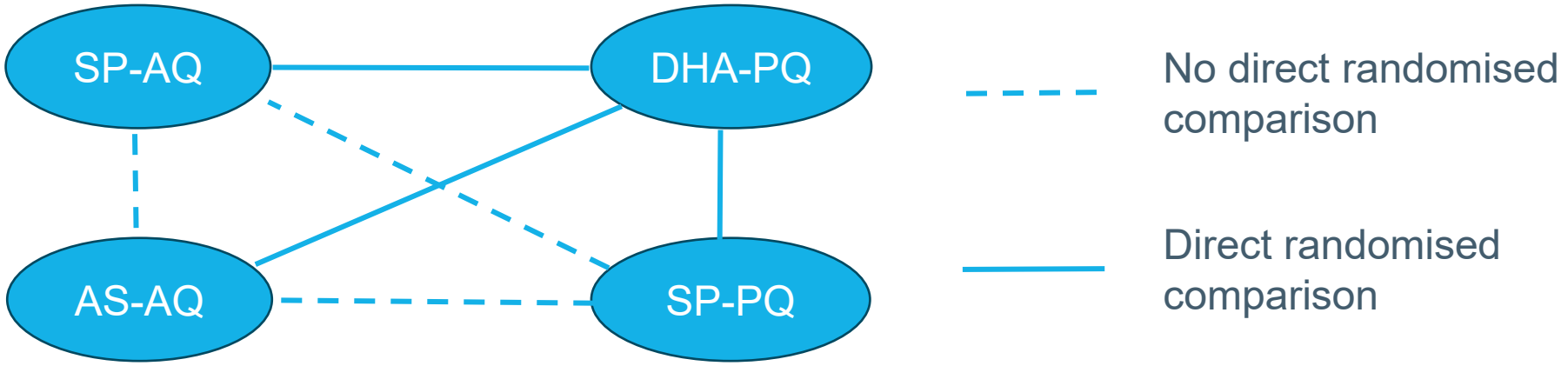
Vaccines

- Co-implementation with SMC in seasonal settings



Network meta-analysis

- Most antimalarial regimens for SMC lack head-to-head randomised comparisons
- Provide indirect evidence on comparative efficacy of an antimalarial in the absence of direct evidence
- Allows comparison of treatments not previously compared – useful for decision-making!



Optimal choice of long-acting antimalarial regimens for SMC

Objectives

- Determine the relative efficacies of long-acting drugs used in SMC against uncomplicated and severe malaria
- Rank treatments based on their efficacy to determine the long-acting antimalarial regimen

Methods

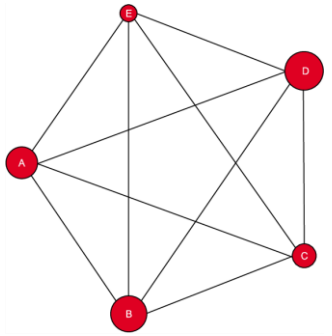
Systematic review
RCTs of SMC

PROSPERO
CRD420251126777

Outcomes
Uncomplicated clinical malaria

Severe malaria

Aggregate-level network meta-analysis



Systematic review: Eligibility criteria

Source: WWARN Malaria Chemoprevention Evidence Map

Inclusion

Intervention

- ✓ Anti-malarial given at regular intervals ('cycles') during high malaria transmission periods during a calendar year.

Outcomes

- ✓ Uncomplicated malaria
- ✓ Severe malaria
- ✓ All-cause mortality

Study Design

- ✓ RCTs (SMC must be randomised)

Exclusion

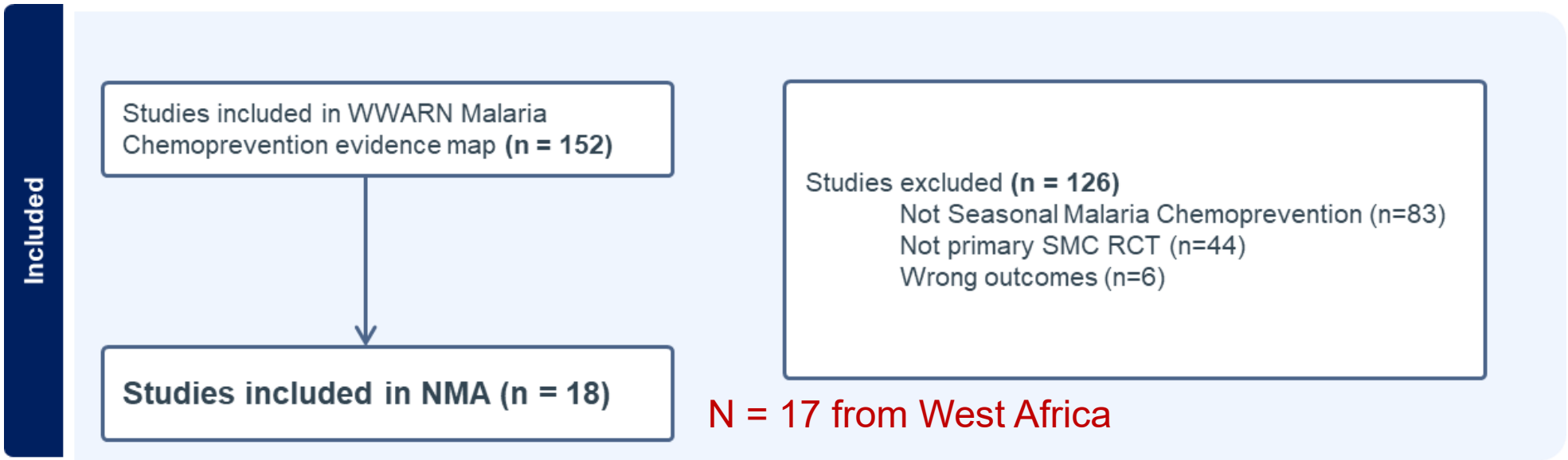
Intervention

- Anti-malarial given at regular intervals beyond periods of high malaria transmission
- Anti-malarial given in periods not coincident with high malaria transmission seasons
- PMC / IPTi / IPT in individuals with sickle cell disease / IPT in school aged children

Study Design

- Non-RCTs

Systematic review: Findings



36,199 participants and one stepped-wedge cRCT with 14,000, 90,000 and 160,000 participants over three consecutive years

Data extraction and synthesis

Transitivity

- Microscopy vs RDT sensitivity
- Variable follow-up period and waning SMC efficacy

Treatment arms were grouped into NMA nodes based on distinct long-acting antimalarials:

- **Sulphadoxine-pyrimethamine**
- **Amodiaquine**
- **Piperaquine**
- **Seasonal RTS,S vaccination**

Statistical analysis

Uncomplicated malaria

Bayesian hierarchical network meta-analysis model (*gemtc* and *rjags* in R)

- Input: logIRR and standard errors for each treatment contrast per study
- Likelihood = Normal; Link = Identity
- Random effects and common effect models
- Network estimates (IRR) and treatment ranking of all treatment comparisons against uncomplicated malaria

Node-splitting to assess for inconsistency

Pairwise meta-analyses, subgroup analyses and meta-regression to investigate for sources of treatment effect heterogeneity

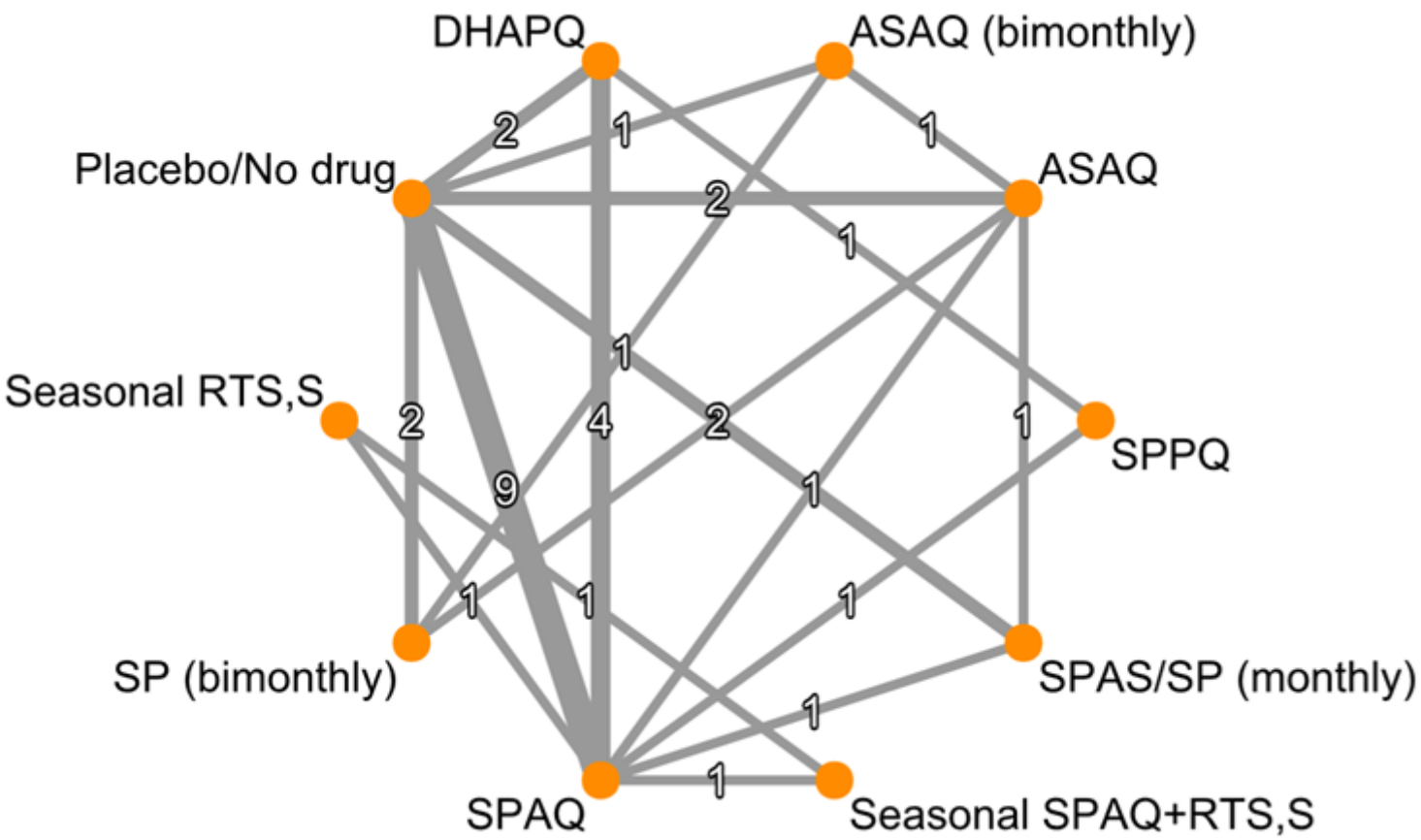
- SMC supervision; SP resistance; Study design

Sensitivity analyses

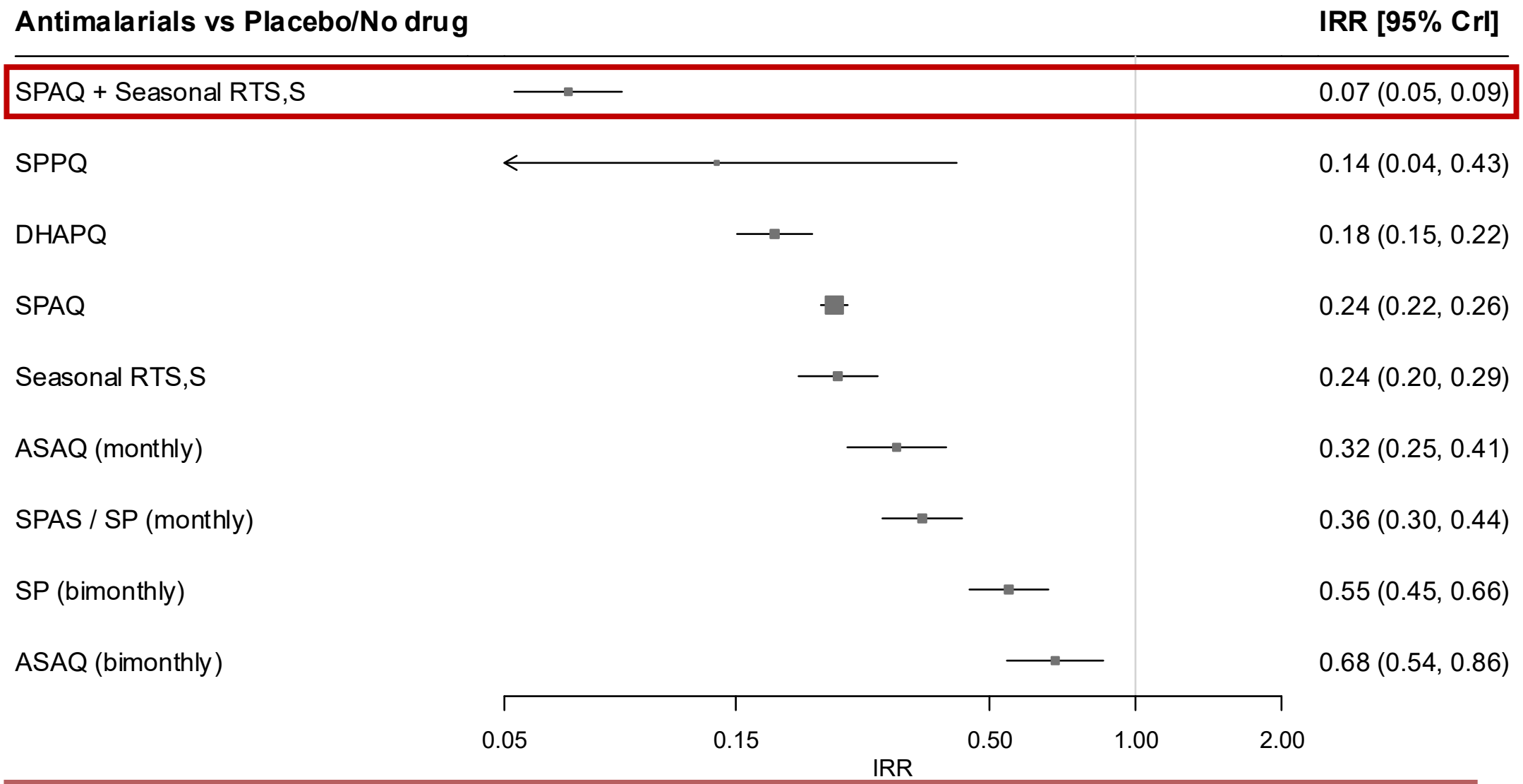
- Under-five only; West Africa only

Results: Network plot

Uncomplicated clinical malaria

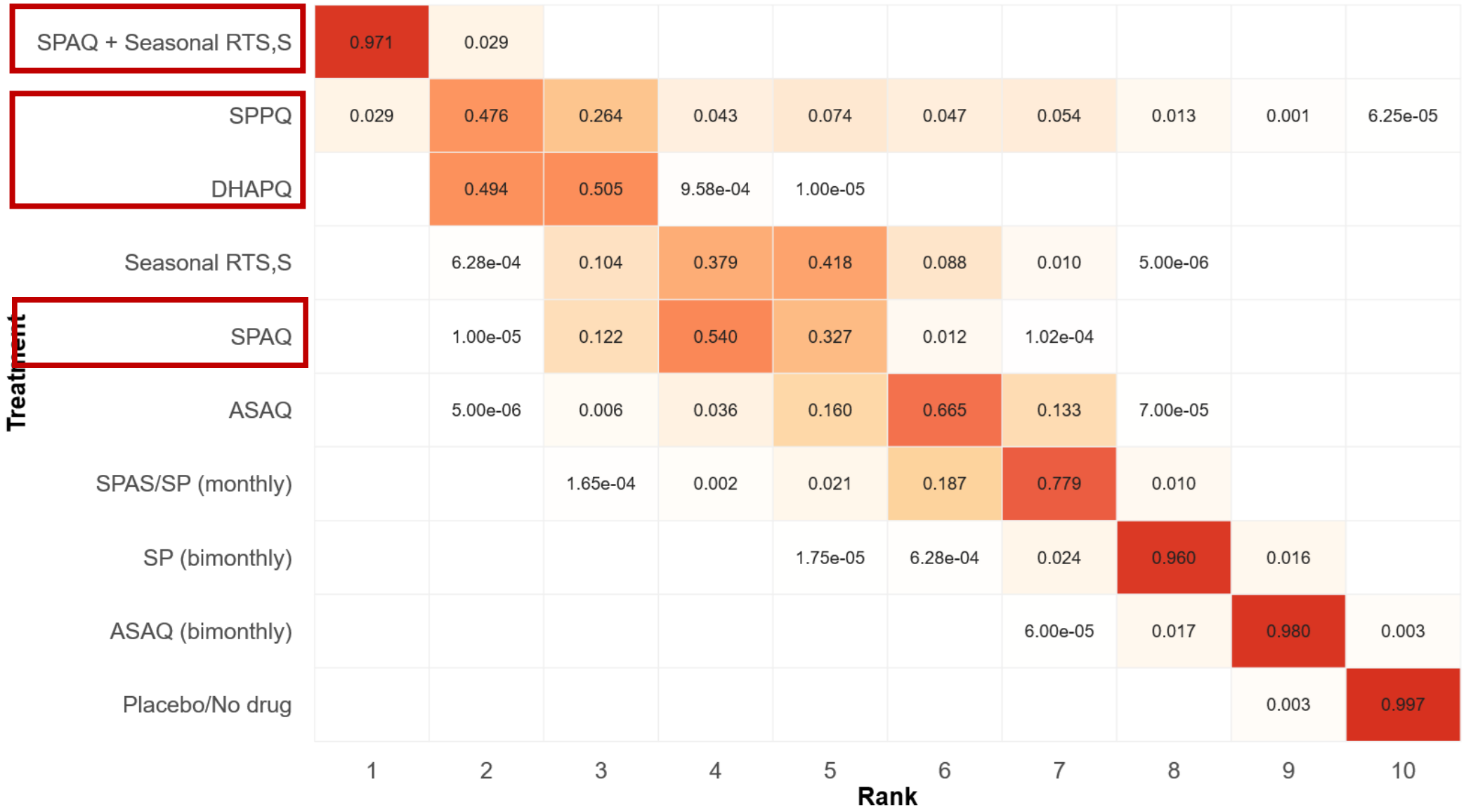


Network estimates vs placebo/no SMC



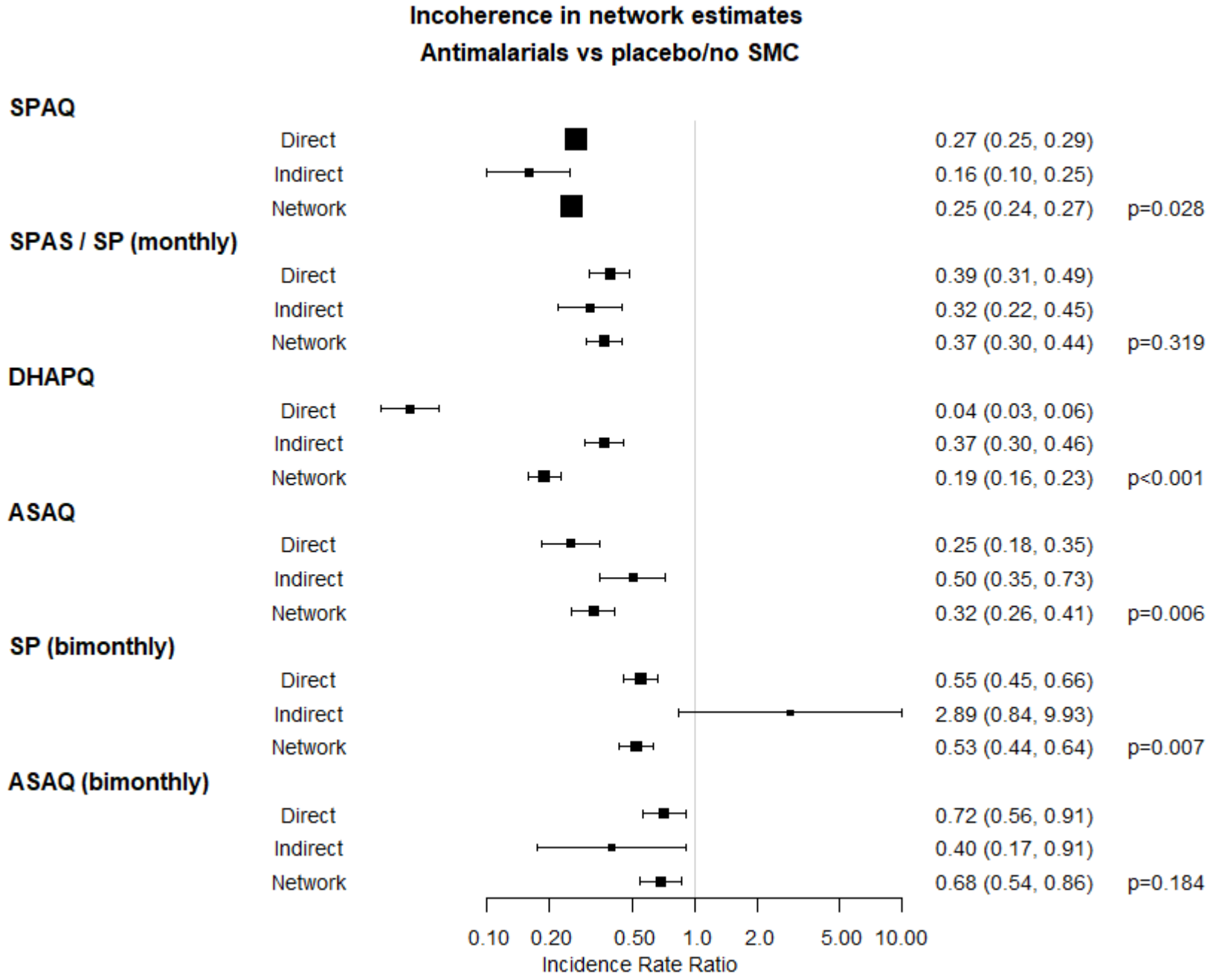
Common effect model
Within-design heterogeneity; Q = 106.33; p-value < 0.0001; I^2 93.8%

Treatment ranking

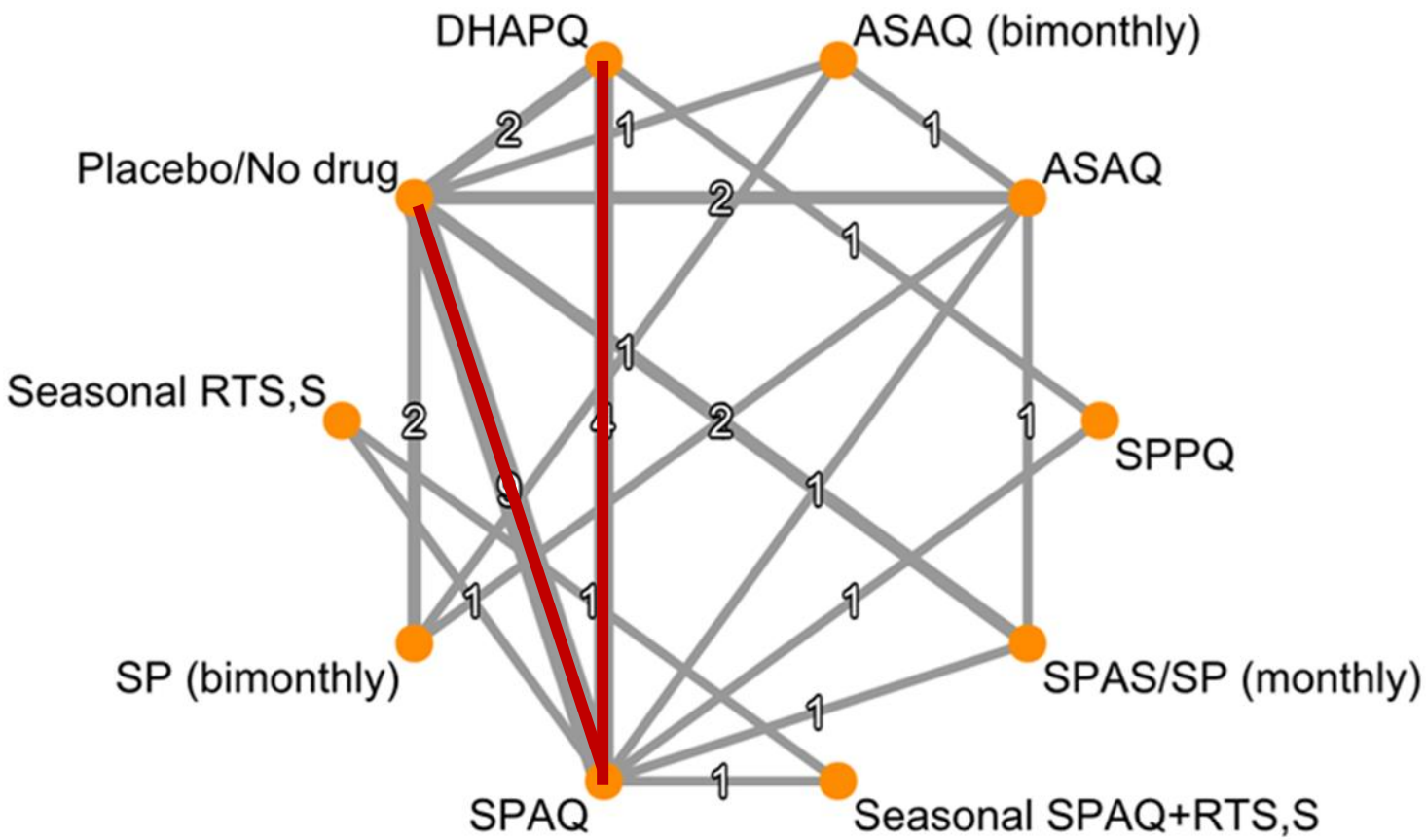


Incoherence

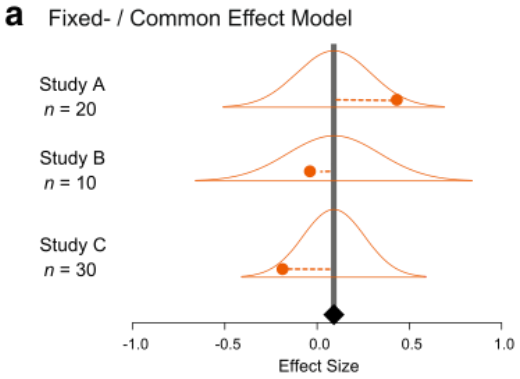
Direct vs Indirect vs Network

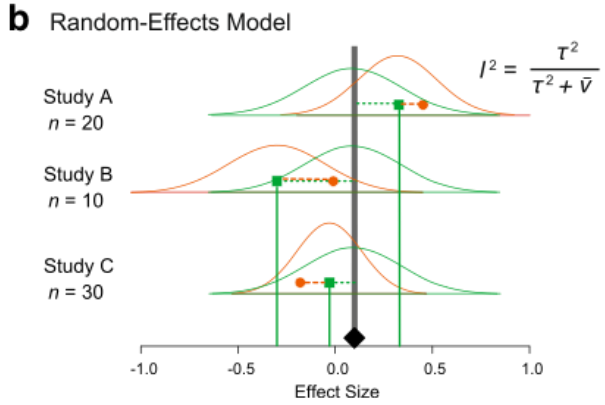


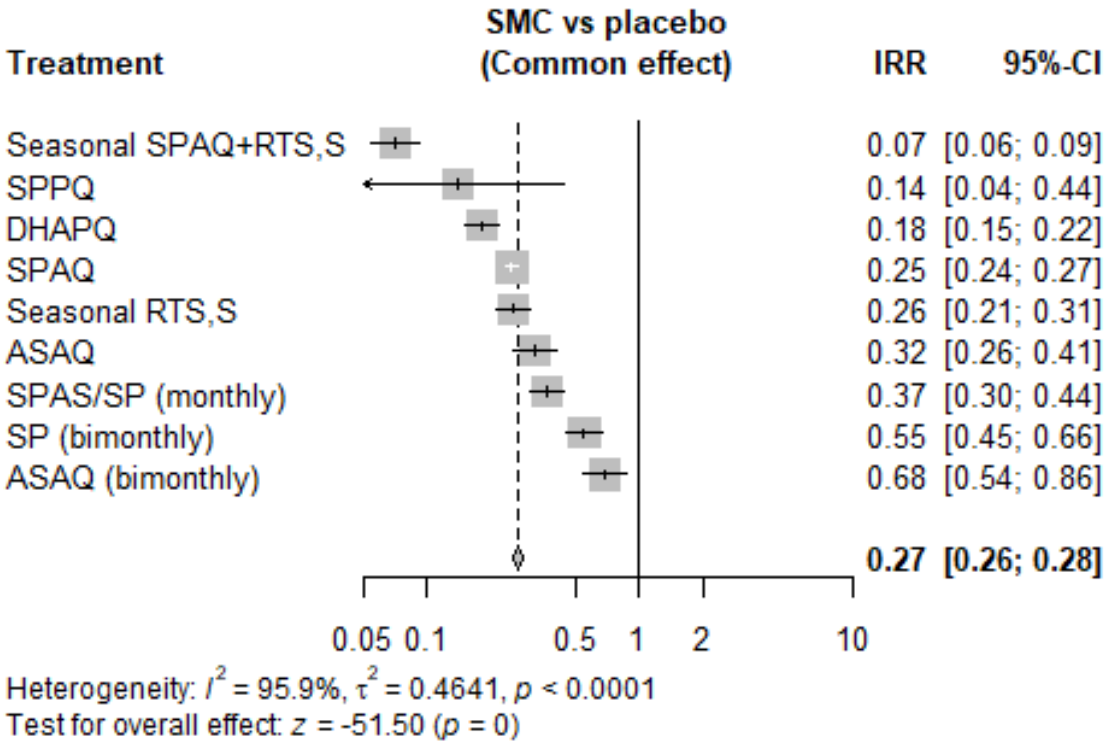
Investigating heterogeneity (Subgroup analyses + Meta-regression)

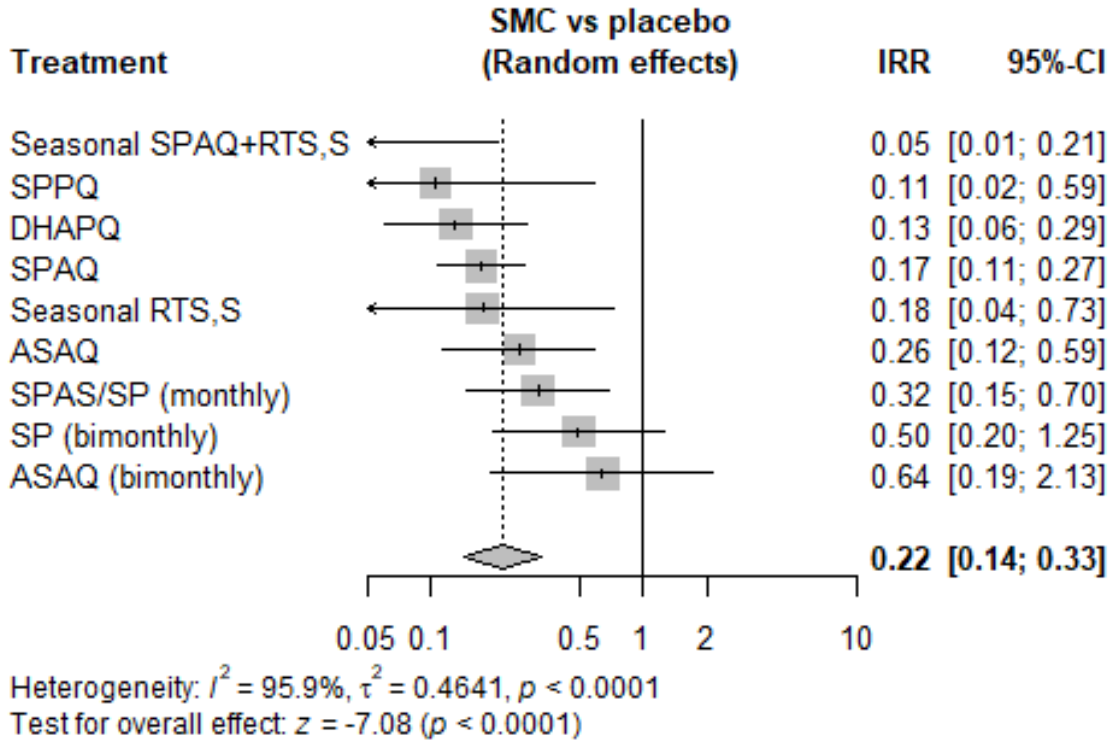


Choice of statistical model: CE vs RE?

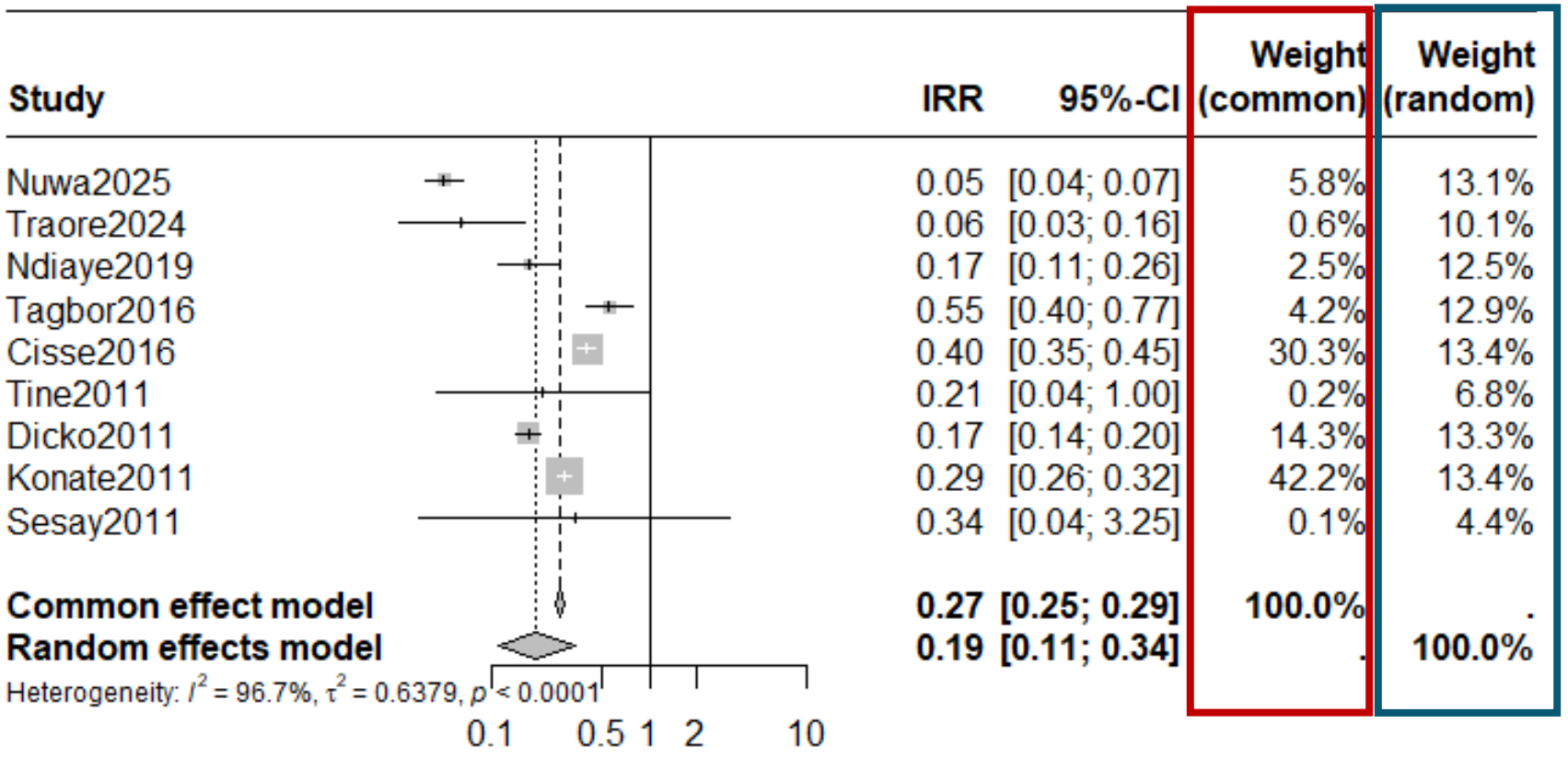






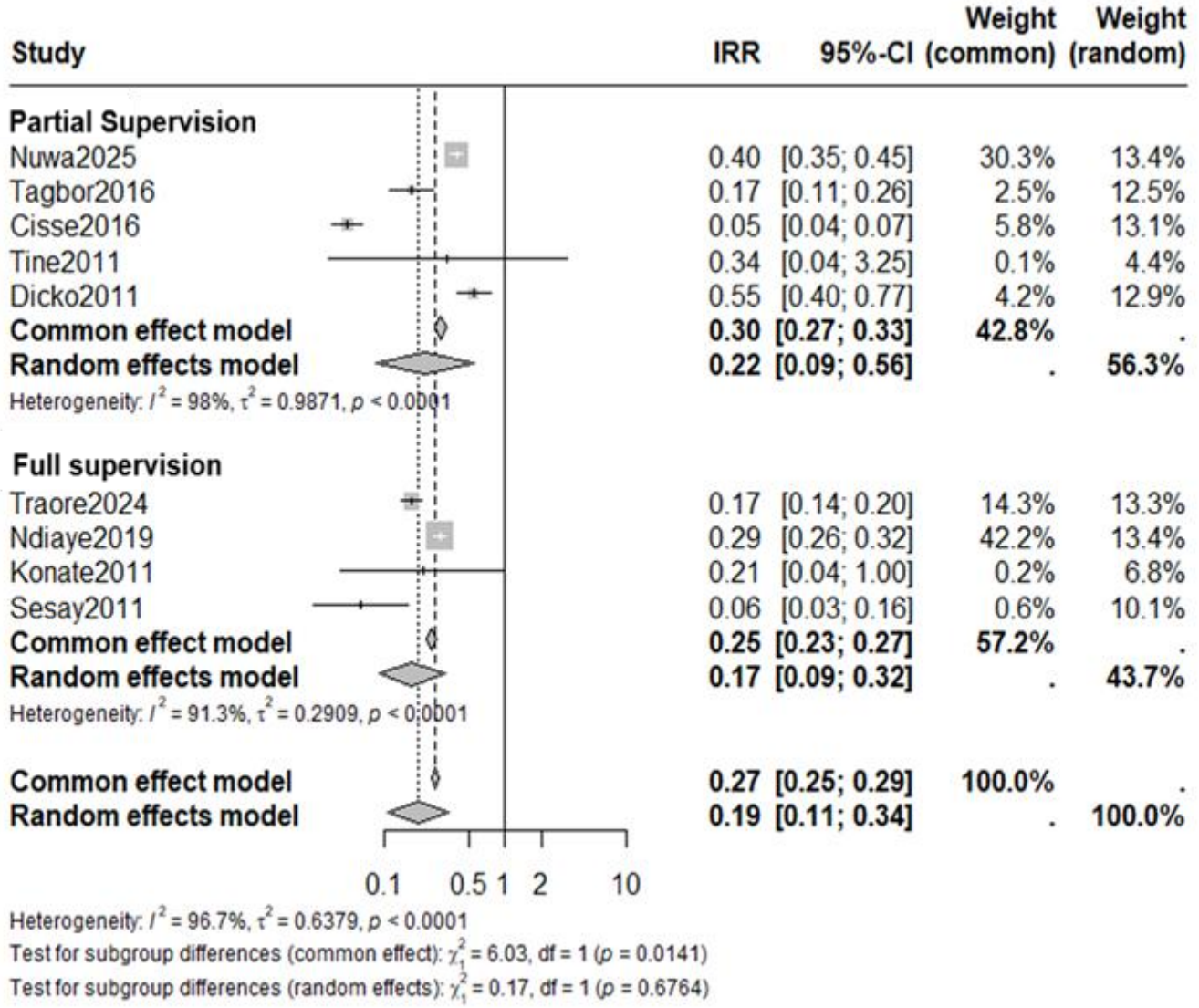


Pairwise meta-analysis: SPAQ vs placebo/no SMC



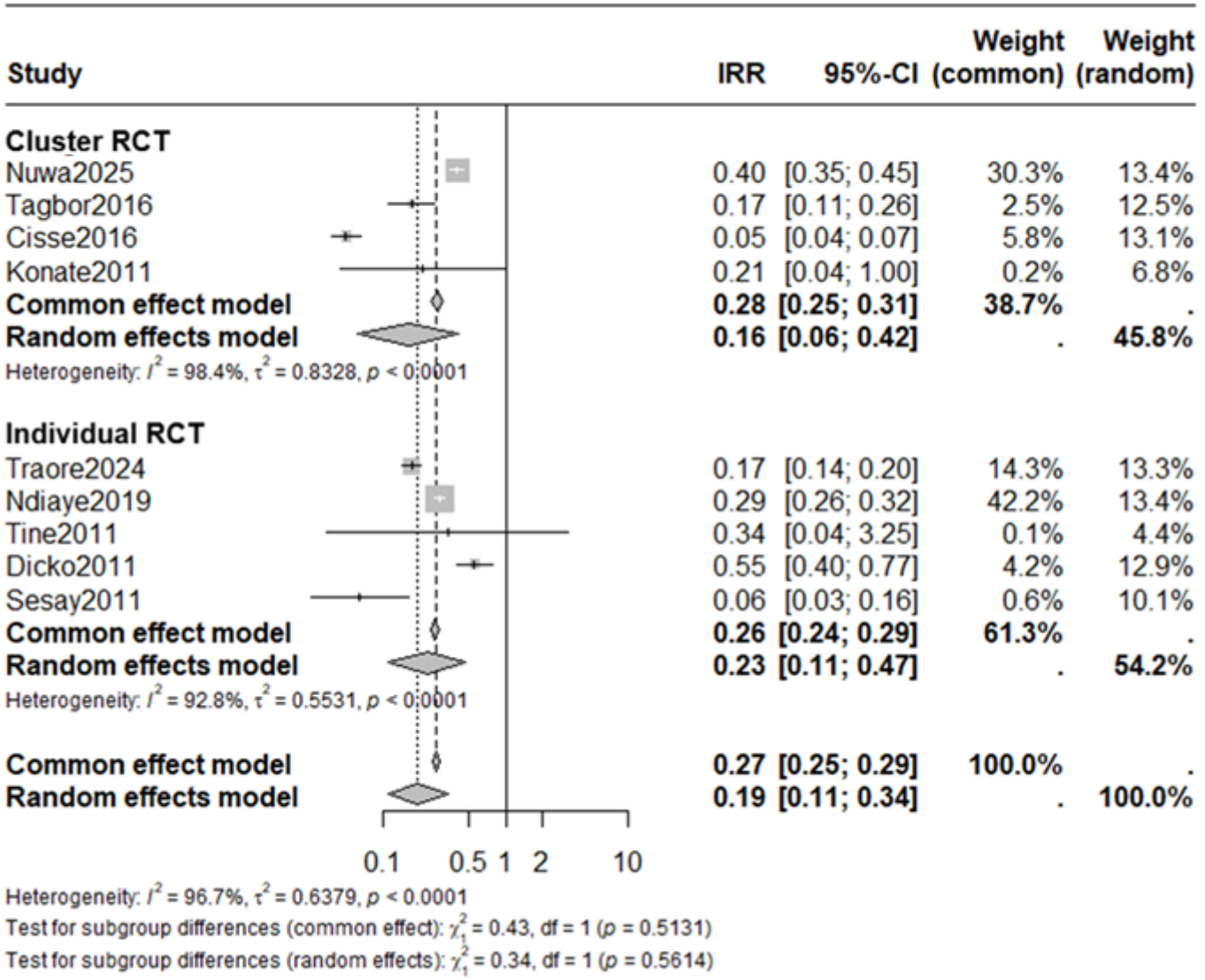
SPAQ vs placebo/no SMC by SMC supervision

Network meta-regression	SMC Supervision Full vs partial supervision
Beta (95% CrI)	0.89 (0.79, 1.00)
DIC (parent model)	393.12033
DIC (nested covariate model)	388.0126
ΔDIC	5.10773



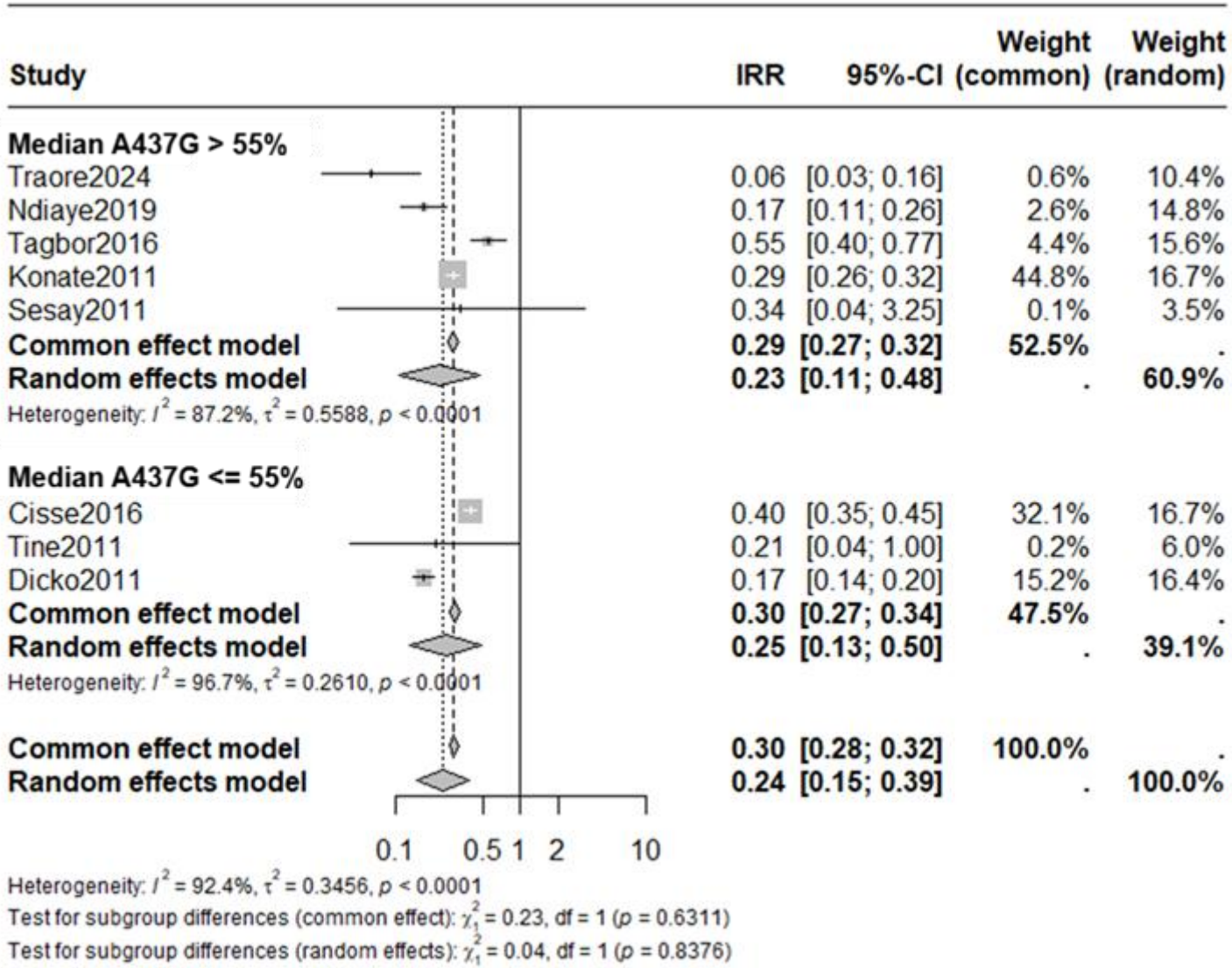
SPAQ vs placebo/no SMC by study design

Network meta-regression	Study design cRCT vs iRCT
Beta (95% CrI)	0.96 (0.84, 1.10)
DIC (parent model)	393.12033
DIC (nested covariate model)	394.44681
ΔDIC	-1.32648



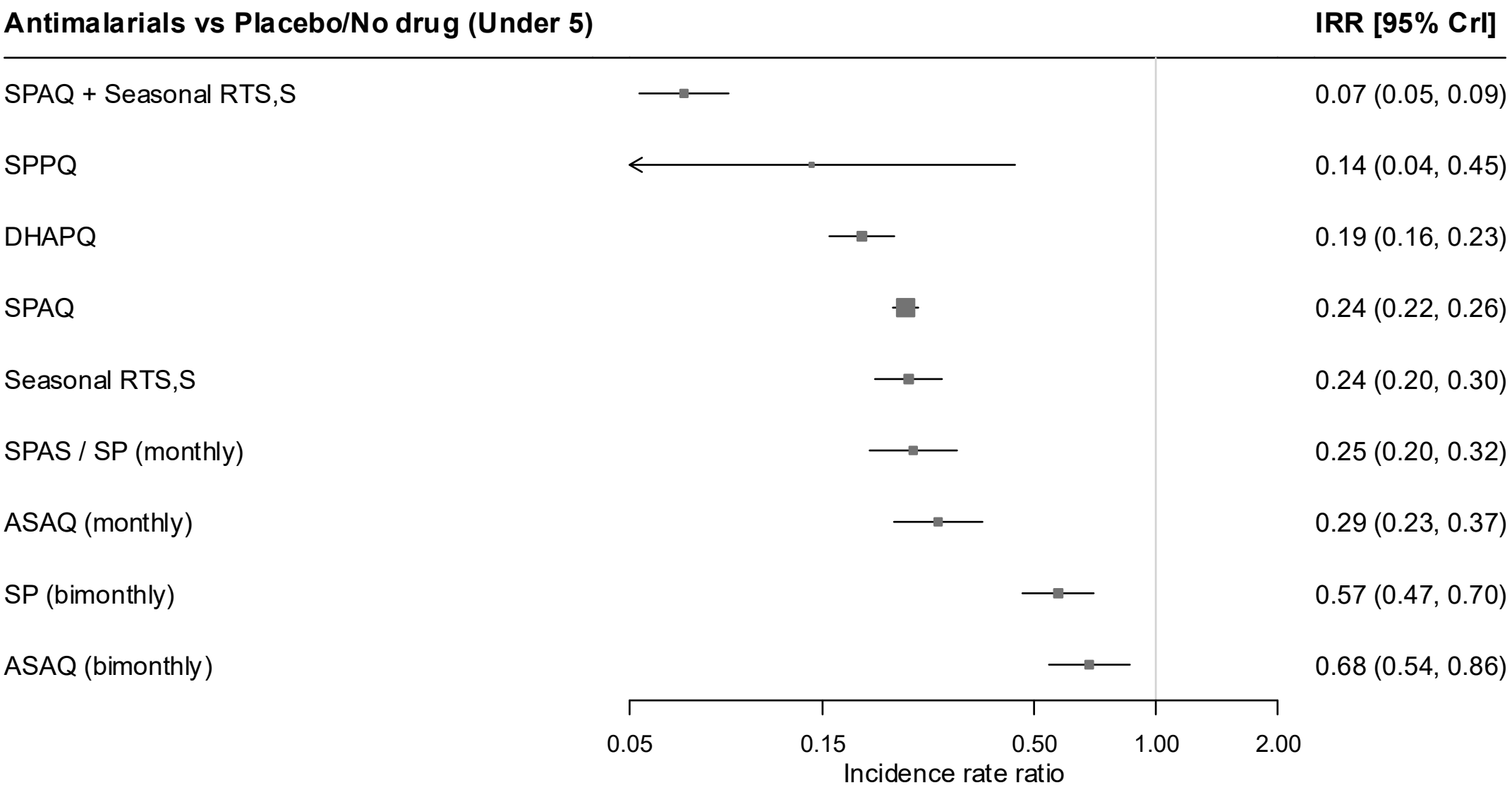
SPAQ vs placebo/no SMC by prevalence of A437G mutation

Network meta-regression	Prevalence of A437G mutation High vs Low
Beta (95% CrI)	1.01 (0.89, 1.15)
DIC (parent model)	174.250444
DIC (nested covariate model)	176.199313
ΔDIC	-1.948869

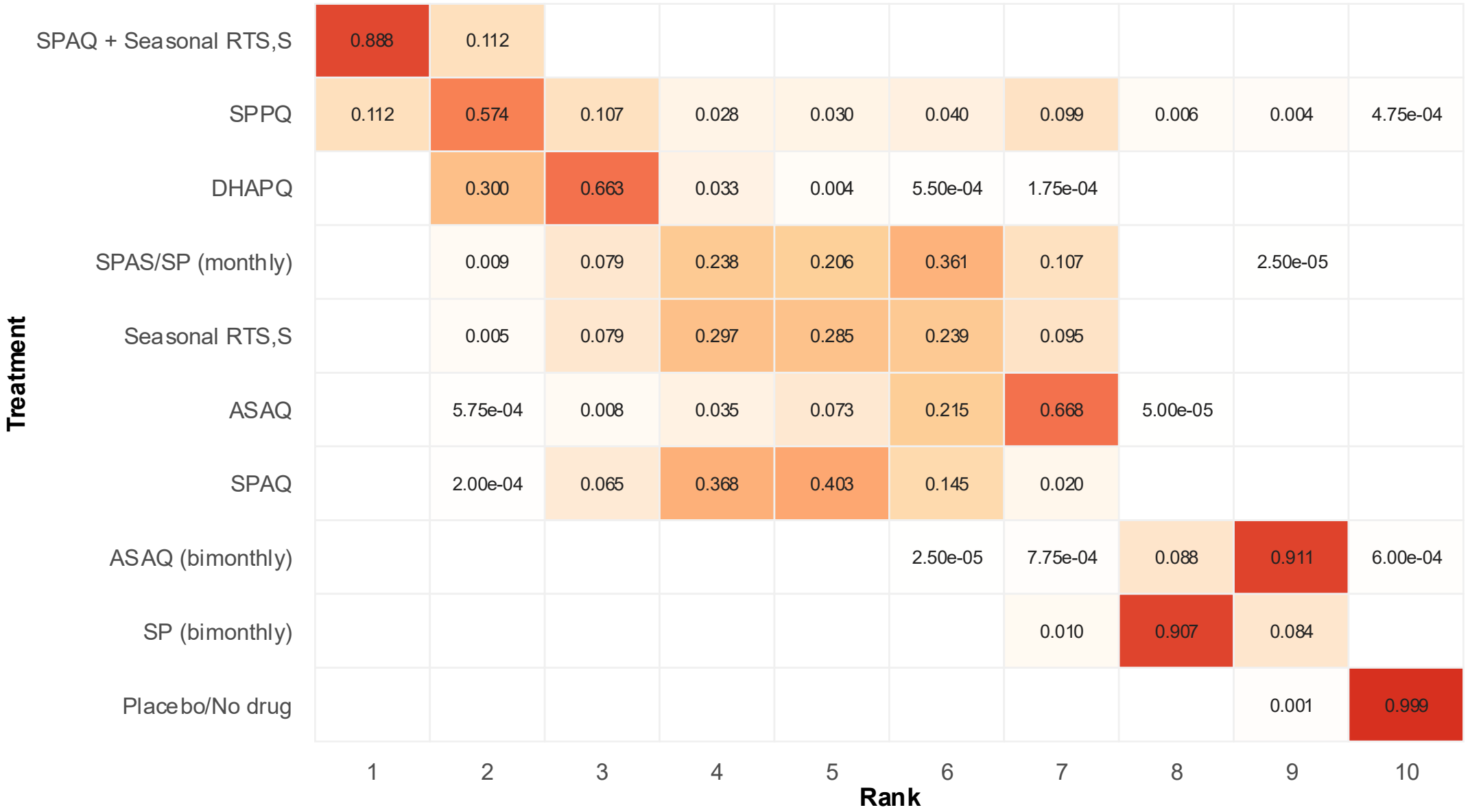


Sensitivity analyses

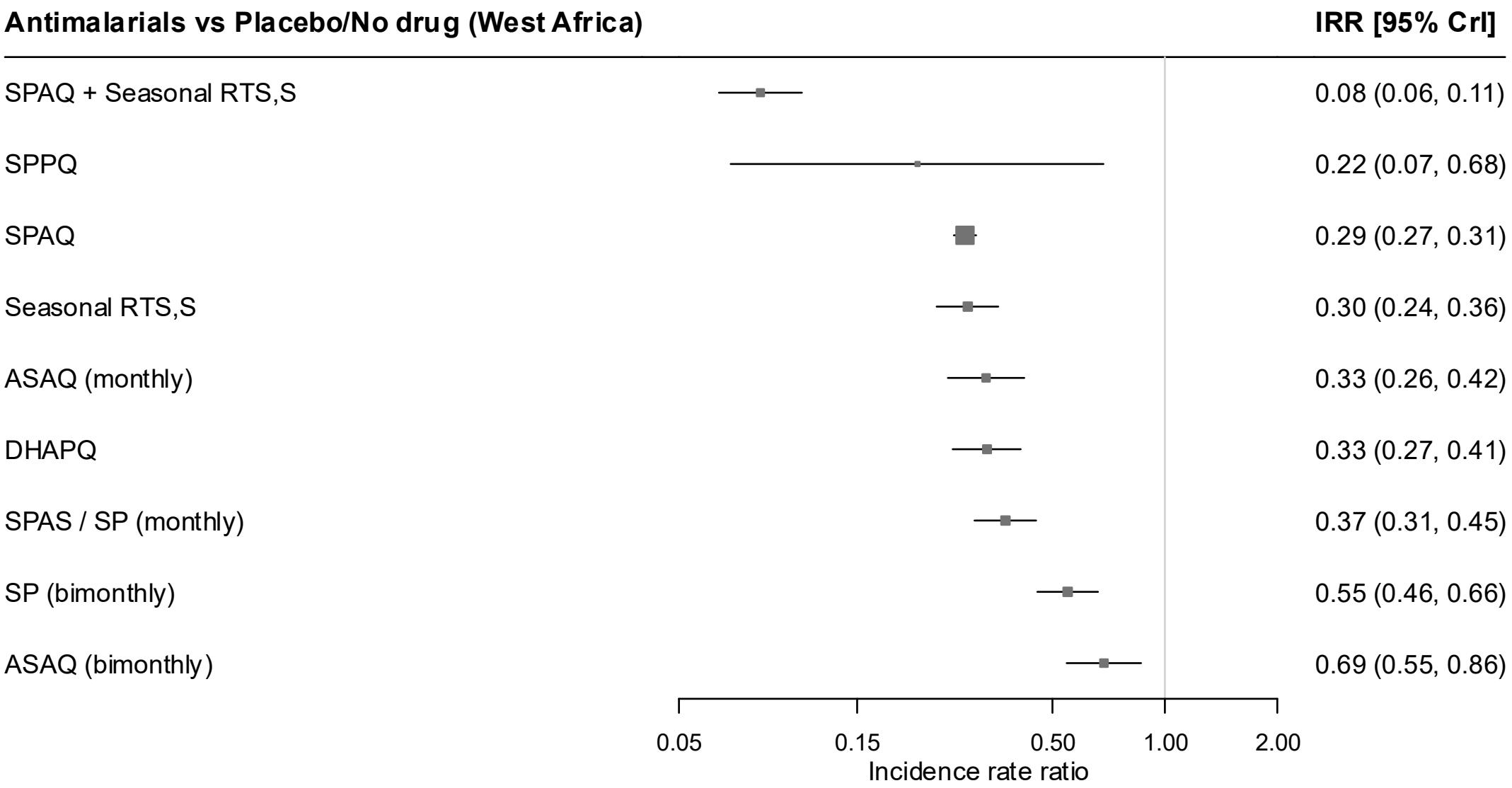
Under five children only: Relative efficacies



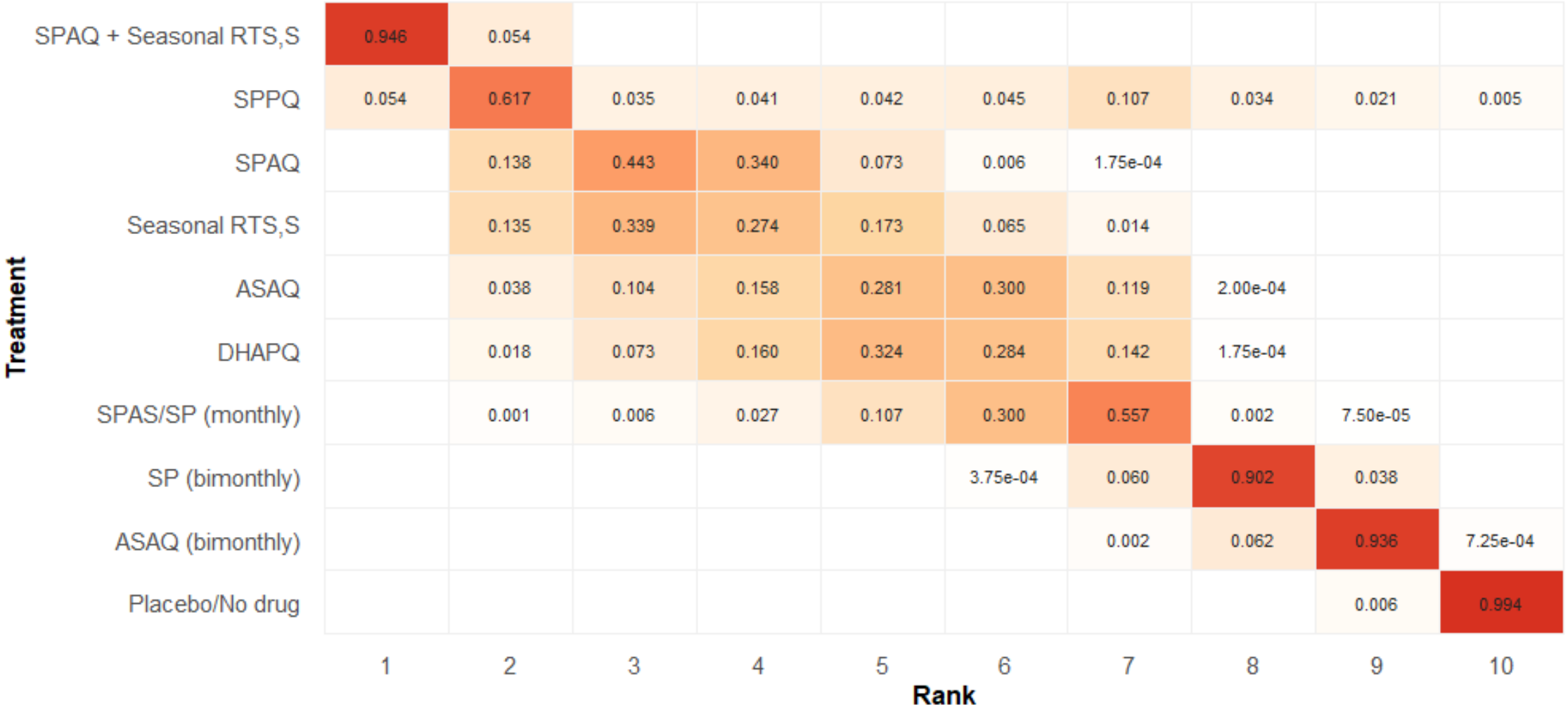
Under five children only: Treatment ranking



West Africa only



West Africa only: Treatment ranking



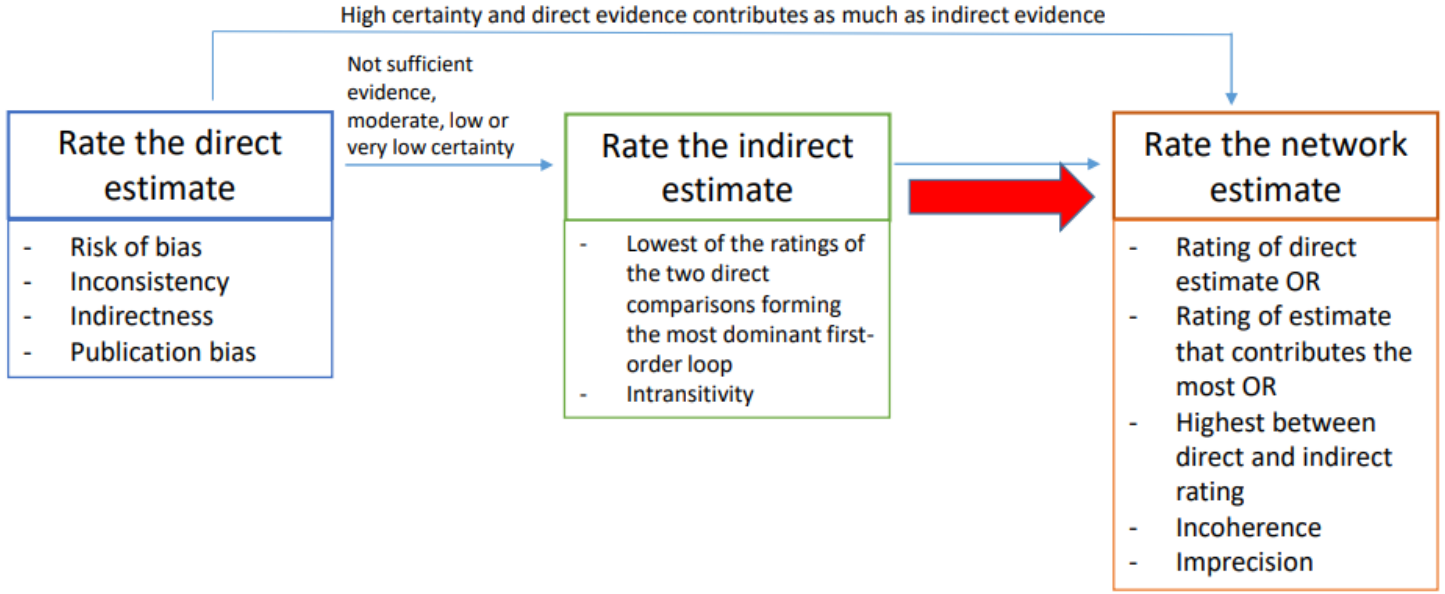
Node-splitting:

	DP vs placebo (All trials)	DP vs placebo (West Africa only)
direct	0.04 (0.03, 0.6)	0.07 (0.03, 0.15)
indirect	0.37 (0.30, 0.46)	0.37 (0.30, 0.46)
network	0.19 (0.16, 0.23)	0.33 (0.27, 0.41)

GRADE quality of evidence rating

Domains:

- Within-study risk of bias
- Within-design heterogeneity (inconsistency)
- Indirectness (transitivity)
- Publication bias
- Incoherence (direct vs indirect evidence)
- Imprecision



Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, Hazlewood GS, Alhazzani W, Mustafa RA, Murad MH, Puhan MA, Schünemann HJ, Guyatt GH; GRADE Working Group. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol. 2018 Jan;93:36-44. doi: 10.1016/j.jclinepi.2017.10.005. Epub 2017 Oct 17. Erratum in: J Clin Epidemiol. 2018 Jun;98:162. doi: 10.1016/j.jclinepi.2018.04.013. PMID: 29051107.

Risk of Bias assessment

Cluster RCTs Study ID	D1a	D1b	D2	D3	D4	D5	Overall ROB
Nuwa 2025	-	+	-	+	-	+	-
Ndiaye 2019	+	+	+	+	+	+	+
Cisse 2016	+	+	+	+	+	+	+
Tine 2011	!	+	+	+	-	!	-

Key	
D1a	Randomisation process
D1b	Timing of identification or recruitment of participants
D2	Deviations from the intended interventions
D3	Missing outcome data
D4	Measurement of the outcome
D5	Selection of the reported result

Individual RCTs Study ID	D1	D2	D3	D4	D5	Overall ROB
Traore 2024	+	+	+	+	+	+
Chandramohan 2021	+	+	+	+	+	+
Thera 2018	+	+	+	-	+	-
Tagbor 2016	+	+	+	+	+	+
Zongo 2015	+	+	+	+	+	+
Dicko 2011	+	+	+	+	+	+
Konate 2011	+	+	+	+	+	+
Sesay 2011	+	+	+	+	+	+
Bojang 2010 (b)	+	+	+	+	+	+
Bojang 2010 (a)	+	+	+	+	+	+
Sokhna 2008	!	+	+	+	+	!
Dicko 2008	+	+	+	-	+	-
Kweku 2008	+	+	+	+	+	+
Cisse 2006	+	+	+	+	+	+

Key	
D1	Randomisation process
D2	Deviations from the intended interventions
D3	Missing outcome data
D4	Measurement of the outcome
D5	Selection of the reported result

GRADE quality of evidence rating

Intervention (vs placebo/no SMC)	Direct estimate	Reasons for downgrading	Indirect estimate	Reasons for downgrading	Network estimate	Reasons for downgrading
Seasonal RTS,S + SPAQ	Nil		Low	Major concern: Within-design heterogeneity	**Low**	
SPPQ	Nil		Low	Major concern: Within-design heterogeneity	**Low**	
DHAPQ	Moderate	Some concerns: ROB	Low	Major concern: Within-design heterogeneity	**Very Low**	Major concern: Incoherence
SPAQ	Low	Major concern: Within-design heterogeneity	Moderate	Some concerns: ROB	**Low**	
Seasonal RTS,S	Nil		Low	Major concern: Within-design heterogeneity	**Low**	
ASAQ (monthly)	Moderate	Some concerns: ROB	Low	Major concern: Within-design heterogeneity	**Moderate**	
SPAS / SP (monthly)	Moderate	Some concern: Within-design heterogeneity	Low	Major concern: Within-design heterogeneity	**Moderate**	
SP (bimonthly)	Moderate	Some concern: Within-design heterogeneity	Nil		**Moderate**	
ASAQ (bimonthly)	Moderate	Some concern: Within-design heterogeneity	Low	Major concern: Within-design heterogeneity	**Low**	Some concerns: Imprecision

What do the findings mean?

Consistent with mechanistic basis of chemoprevention:

- Longer t1/2 = better protective efficacy

Generalisability: West Africa

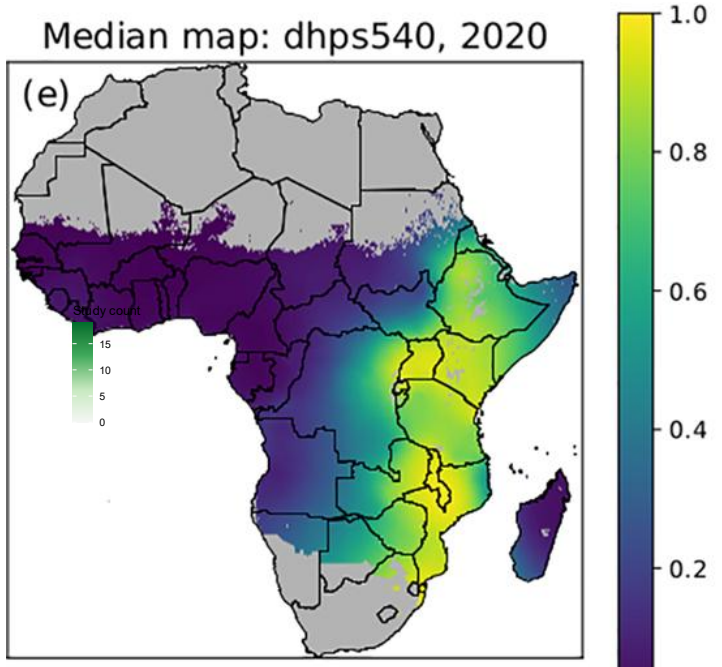
- SP resistance profiles of West & E/S Africa differ
- Inference about East / Southern Africa (esp. non-SP containing regimens)

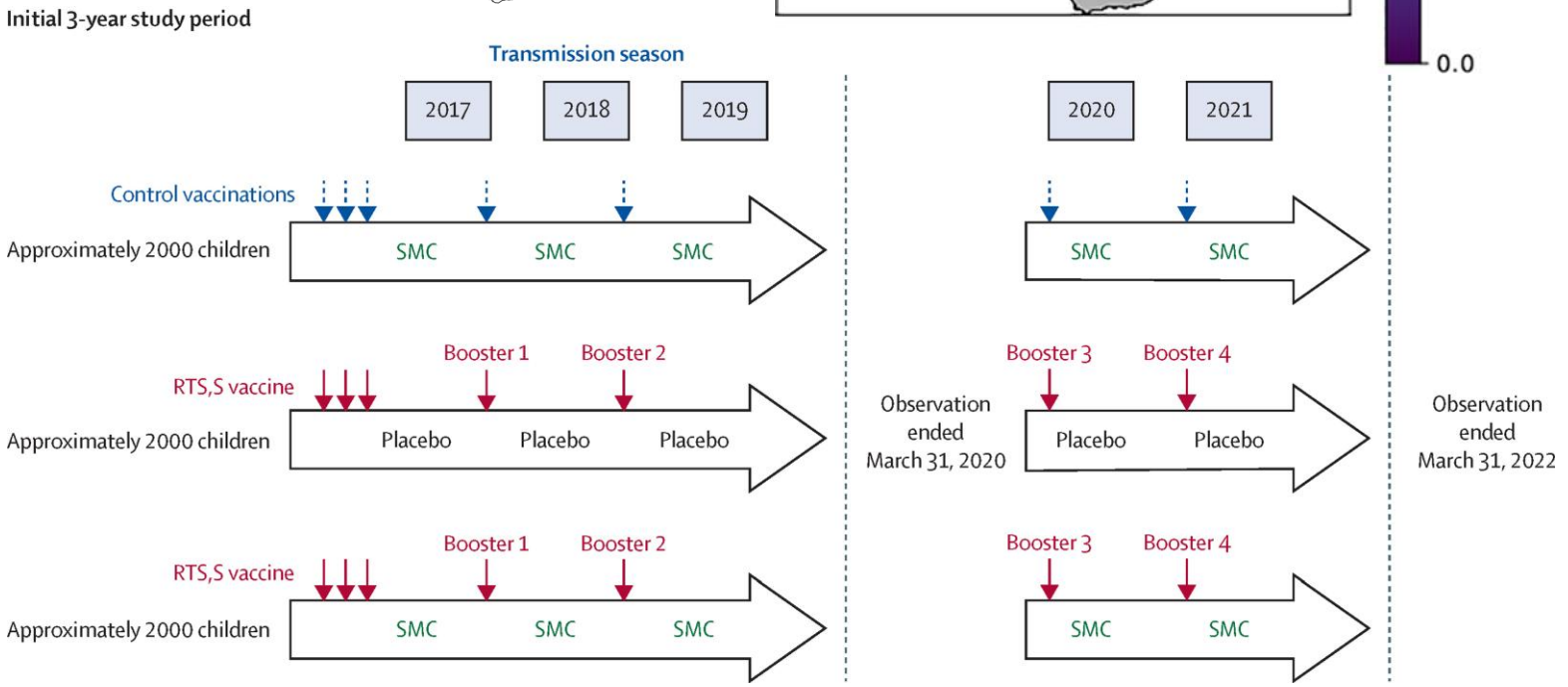
High efficacy of Seasonal RTS,S vaccination + SMC; Log-multiplicative effect

- Cost-effectiveness and implementation

SMC data

SP resistance





Seasonal vaccination with RTS,S/AS01$_E$ vaccine with or without seasonal malaria chemoprevention in children up to the age of 5 years in Burkina Faso and Mali: a double-blind, randomised, controlled, phase 3 trial Dicko, Alassane et al. The Lancet Infectious Diseases, Volume 24, Issue 1, 75 - 86

What do the findings mean?

PQ-based SMC may be > AQ-based SMC

DHA-PQ and SPPQ could be alternatives

Where?

Considerations:

- Weight-based dosing for PQ
- Better adherence (vs AQ)
- Cost-effectiveness of PQ-based SMC
- PQ-based treatment

What do the findings mean?

- Substantial treatment effect heterogeneity, remains largely unexplained using aggregate data
- Limitations using aggregate data:
  - Outcome standardisation
  - Subgroup analyses and MR have low power
  - Could not include all eligible trials due to inadequate outcome reporting

Summary

- PQ-based SMC may be an alternative to AQ-based SMC
  - Need much more data
  - Further optimised by combining with seasonal vaccination
- Quality of evidence was generally low, due to heterogeneity and incoherence (DP)
- Substantial unexplained Heterogeneity in Treatment Effect, largely from SPAQ studies
- IPD-MA for HTE in SMC is justified to explore HTE and quantify determinants to guide optimal deployment of SMC across other parts of Africa
- Ongoing work on severe malaria

Acknowledgements

Professor Philippe Guerin
Dr. James Watson
Dr. Prabin Dahal

Dr Dhol Samuel Ayuen
Dr. Mary Scott

Thank you

Comments and Questions?

dhruv.darji@wwarn.org

"Millions of children's lives could be saved by an expansion of the SMC policy throughout the African regions of seasonal malaria transmission, if safety and effectiveness can be ensured."

P. Chotsiri, N. J. White and J. Tarning

Pairwise meta-analysis: DHAPQ vs SPAQ