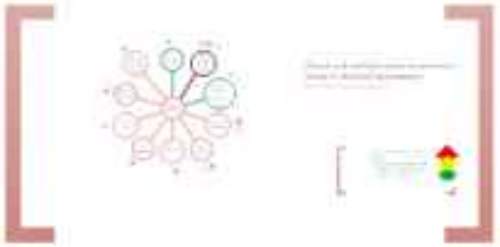

Overview of methods to estimate inconsistency

Sarah Donegan
Department of Biostatistics
University of Liverpool

Catrin Tudur-Smith, Paula Williamson, Umberto D'Alessandro.

Review of methods to assess key assumptions of network meta-analysis

Review of methods to assess key assumptions of network meta-analysis

See the article for full results!

Eligibility

Aim

Search strategy

Results

Aim

We aimed to review and illustrate methods
to assess the homogeneity and consistency assumptions
that have been proposed or applied in methodological articles
focussing on
indirect comparisons or network meta-analysis (NMA).

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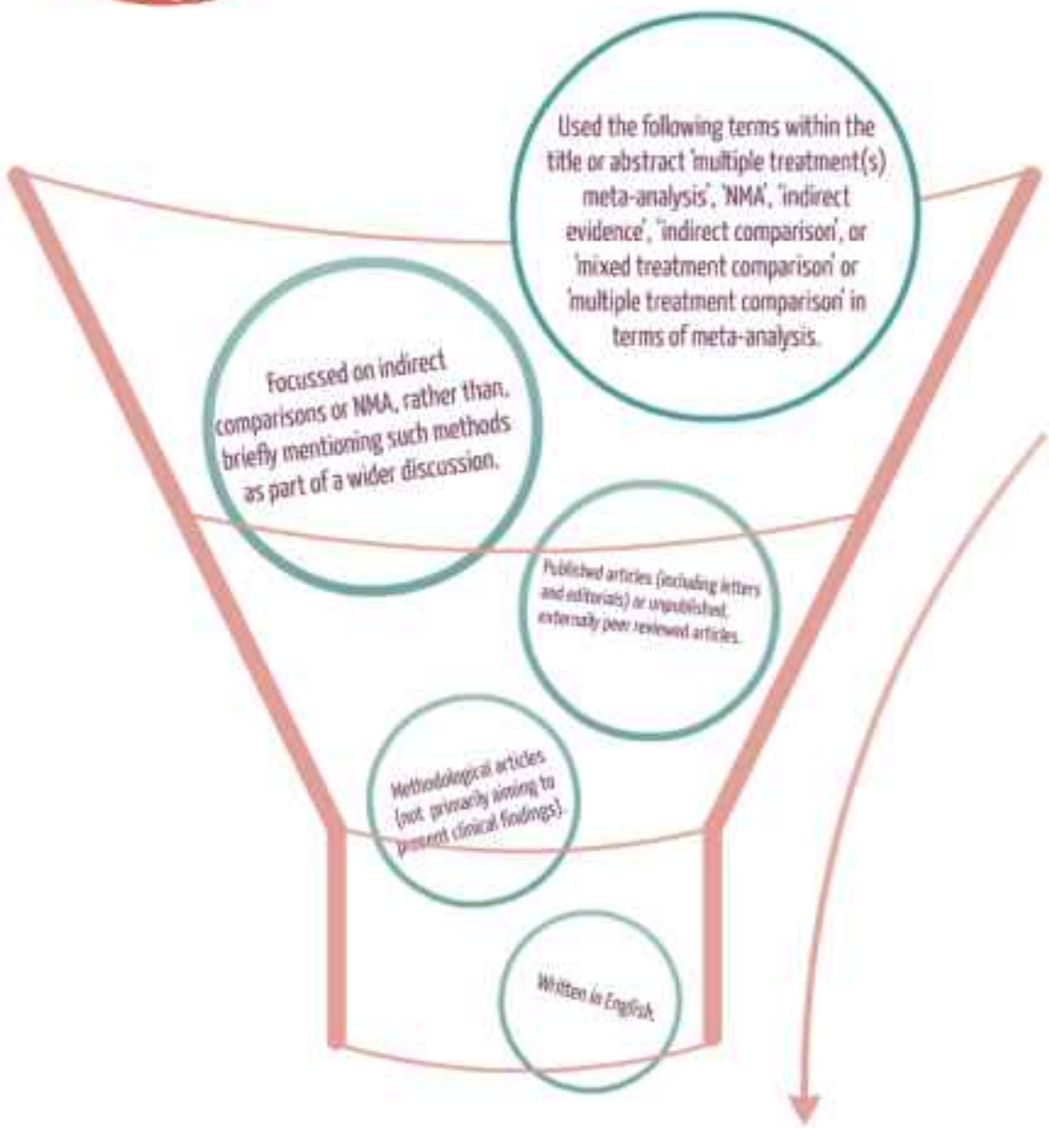

Used the following terms within the title or abstract 'multiple treatment(s) meta-analysis', 'NMA', 'indirect evidence', 'indirect comparison', or 'mixed treatment comparison' or 'multiple treatment comparison' in terms of meta-analysis.

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er than,

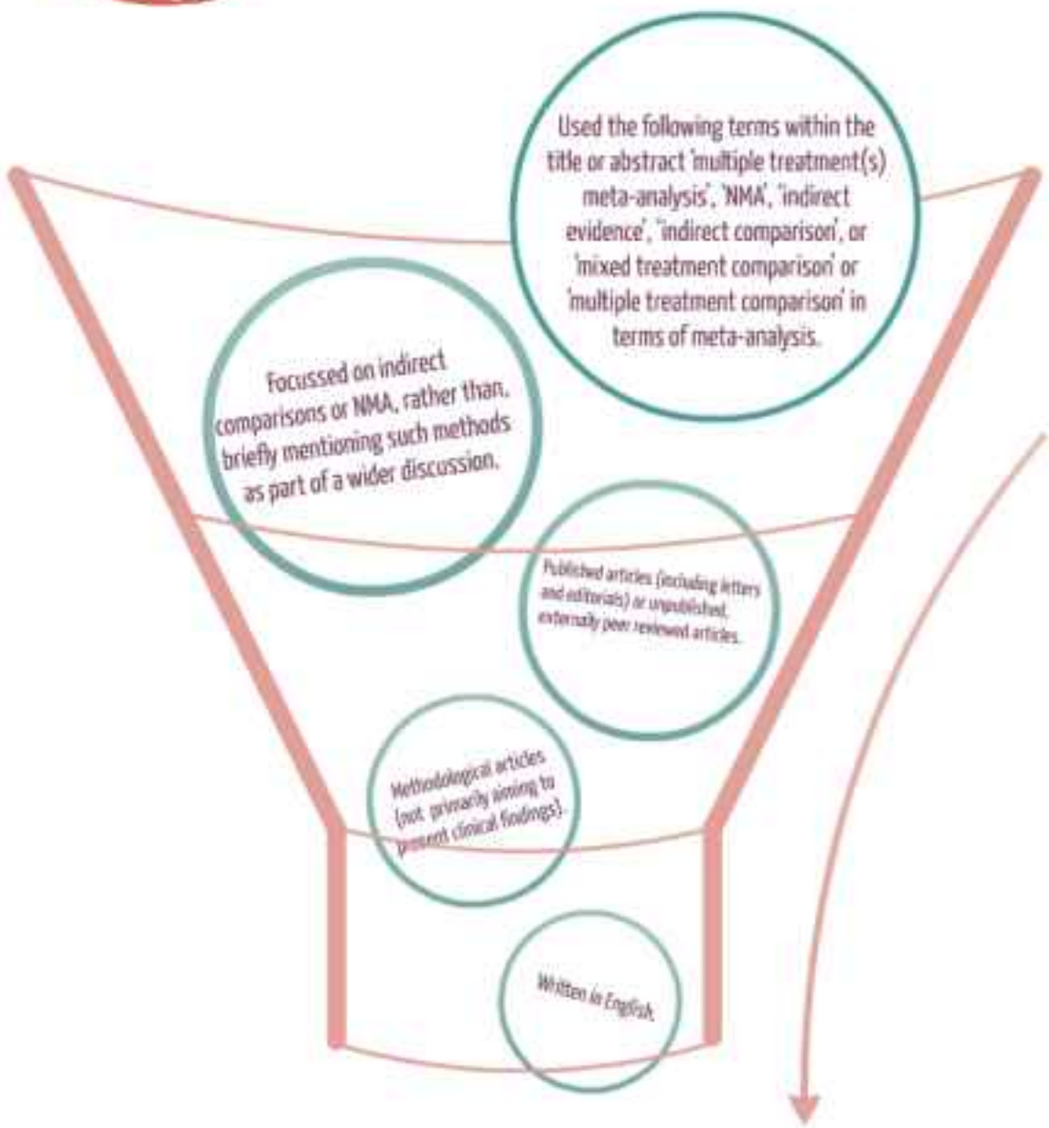
Focussed on indirect comparisons or NMA, rather than, briefly mentioning such methods as part of a wider discussion.

Published articles (including letters and editorials) or unpublished, externally peer reviewed articles.

Methodological articles (not primarily aiming to present clinical findings).

Written in English.

Eligibility



Search strategy

(latest search March 2013)

- handsearching.
- screening the reference lists of included articles.

Results

116 included articles

Abdelhamid et al., 2012; Achana et al., 2013; Ades, 2011; Ades et al., 2012; Ades et al., 2010; Ballesteros, 2005; Bucher et al., 1997; Buti et al., 2011; Caldwell et al., 2005; Caldwell et al., 2007; Caldwell et al., 2010; Caldwell et al., 2012; Chaimani and Salanti, 2012; Chootrakool and Qing Shi, 2008; Chung and Lumley, 2008; Cipriani et al., 2012; Cipriani et al., 2007; Coleman et al., 2012; Cooper et al., 2009; Cooper et al., 2011; Coory and Jordan, 2010; Dakin et al., 2011; Del Giovane et al., 2013; Dewilde and Hawkins, 2012; Dias et al., 2012; Dias et al., 2011a; Dias et al., 2010b; Dias et al., 2010c; Dias et al., 2011b; Dias et al., 2011c; Ding and Fu, 2012; Donegan et al., 2013; Donegan et al., 2012; Donegan et al., 2010; Eckermann et al., 2009; Edwards and Borrill, 2010; Edwards et al., 2009; Fadda et al., 2011; Falissard et al., 2009; Franchini et al., 2012; Gartlehner and Moore, 2008; Glenny et al., 2005; Govan et al., 2010; Griffin et al., 2006; Haute Autorite de Sante, 2009; Hawkins et al., 2010; Hawkins et al., 2009a; Hawkins et al., 2009b; Higgins et al., 2012; Hoaglin et al., 2011; Hong et al., 2013; Ioannidis, 2009; Ioannidis, 2006; Jansen and Cope, 2012; Jansen, 2011; Jansen, 2012; Jansen et al., 2008; Jansen et al., 2011; Jansen et al., 2012; Jonas et al., 2013; Jones et al., 2011; Julious and Wang, 2008; Li et al., 2011; Lu and Ades, 2004; Lu and Ades, 2006; Lu and Ades, 2009; Lu et al., 2007; Lu et al., 2011; Lumley, 2002; Madan et al., 2011; Malone, 2007; Mavridis et al., 2013; Mills et al., 2011a; Mills et al., 2011b; Mills et al., 2012; Naci and Fleurence, 2011; Nixon et al., 2007; Norton et al., 2012; O'Regan et al., 2009; Ouwens et al., 2010; Piepho et al., 2012; Rücker, 2012; Salanti, 2012; Salanti et al., 2011; Salanti et al., 2010; Salanti et al., 2008; Salanti et al., 2009; Salanti and Schmid, 2012; Saramago et al., 2012; Schmidli et al., 2013; Senn et al., 2013; Signorovitch et al., 2012; Song et al., 2003; Song et al., 2012; Song et al., 2000; Song et al., 2008; Song et al., 2009; Song et al., 2011; Spineli et al., 2013; Sturtz and Bender, 2012; Sutton et al., 2008; Thorlund and Mills, 2012a; Thorlund and Mills, 2012b; Thorlund et al., 2013; Trinquart et al., 2012a; Trinquart et al., 2012b; Tudur Smith et al., 2007; Van Valkenhoef et al., 2012a; Van Valkenhoef et al., 2012b; Vandermeer et al., 2007; Wells et al., 2009; Welton et al., 2009; Welton et al., 2008; White et al., 2012; Woods et al., 2010; Xiong et al., 2013).

See the article for full results!

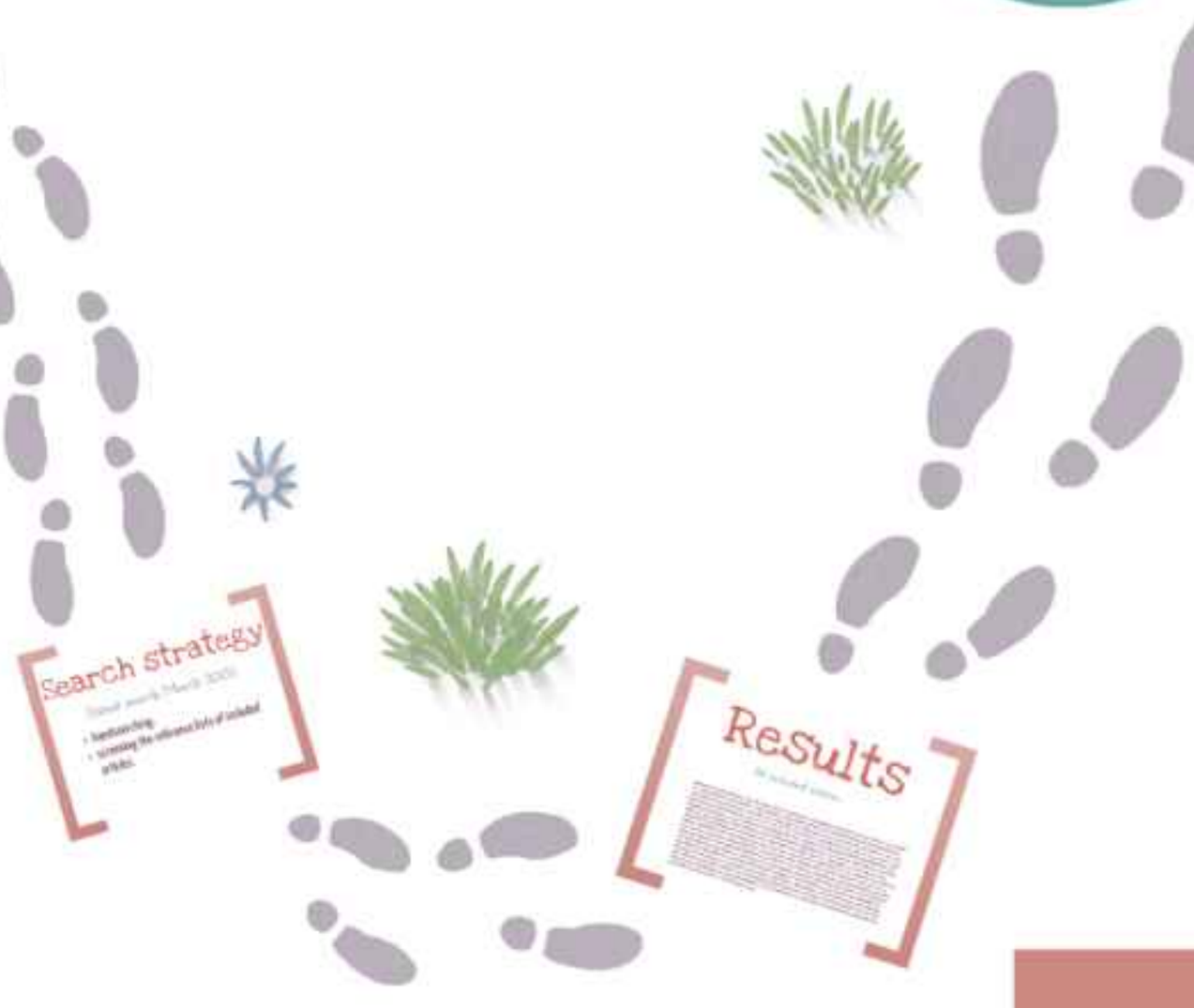
Donegan S, Williamson P, D'Alessandro U, Tudur Smith C. Assessing key assumptions of network meta-analysis: a review of methods. Research synthesis methods (accepted).

Review of methods to assess key assumptions of network meta-analysis

See the article for full results!

Eligibility

Aim



Search strategy

Results

Methods to assess consistency

Methods to assess consistency

Method C1: Comparing patient or trial characteristics

Method C2: Investigating potential treatment effect-modifying covariates

Method C3: Comparing outcome measurements in the referent group

Method C4: Node-splitting (side splitting)

Method C5: Inconsistency models

Method C6: Applying a hypothesis test

Method C7: The back transformation method

Method C8: Multidimensional scaling

Method C9: The two-stage approach

Method C10: The graph-theoretical method

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Clinical and methodological inconsistency
Causes of statistical inconsistency
Statistical inconsistency

Rather than using the methods to classify the assumption as valid or invalid,
a continuous scale of validity should be considered, such that the greater the differences across evidence types, the less likely is consistency.

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Method C3: Comparing outcome measurements in the referent group

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Method C2: Investigating potential treatment effect-modifying covariates

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Rather than using the methods to classify the assumption as valid or invalid,
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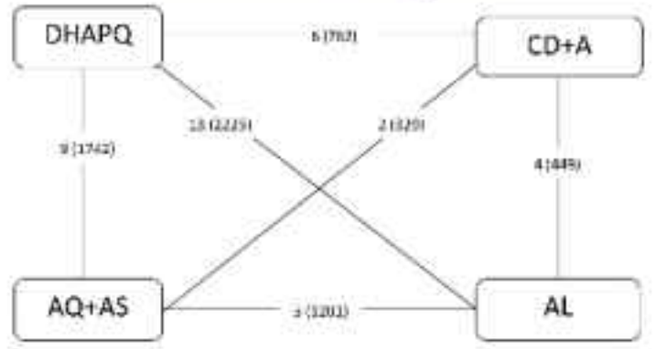
The data: 4abc trial

Network diagram



Number of sites (number of patients).

Design:

Multi-centre randomised trial

Patients:

Children with symptomatic, uncomplicated, plasmodial falciparum mono-infection (malaria).

Interventions:

Four artemisinin combination therapies (anti-malarials).

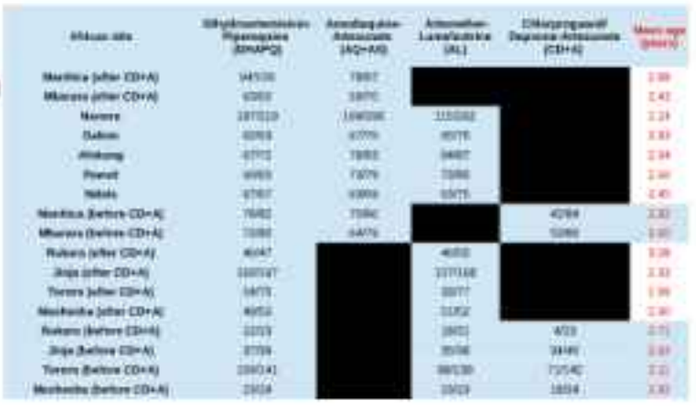
Outcome:

Unadjusted treatment success at day 28.

Covariates:

Patient age, etc

Individual patient data



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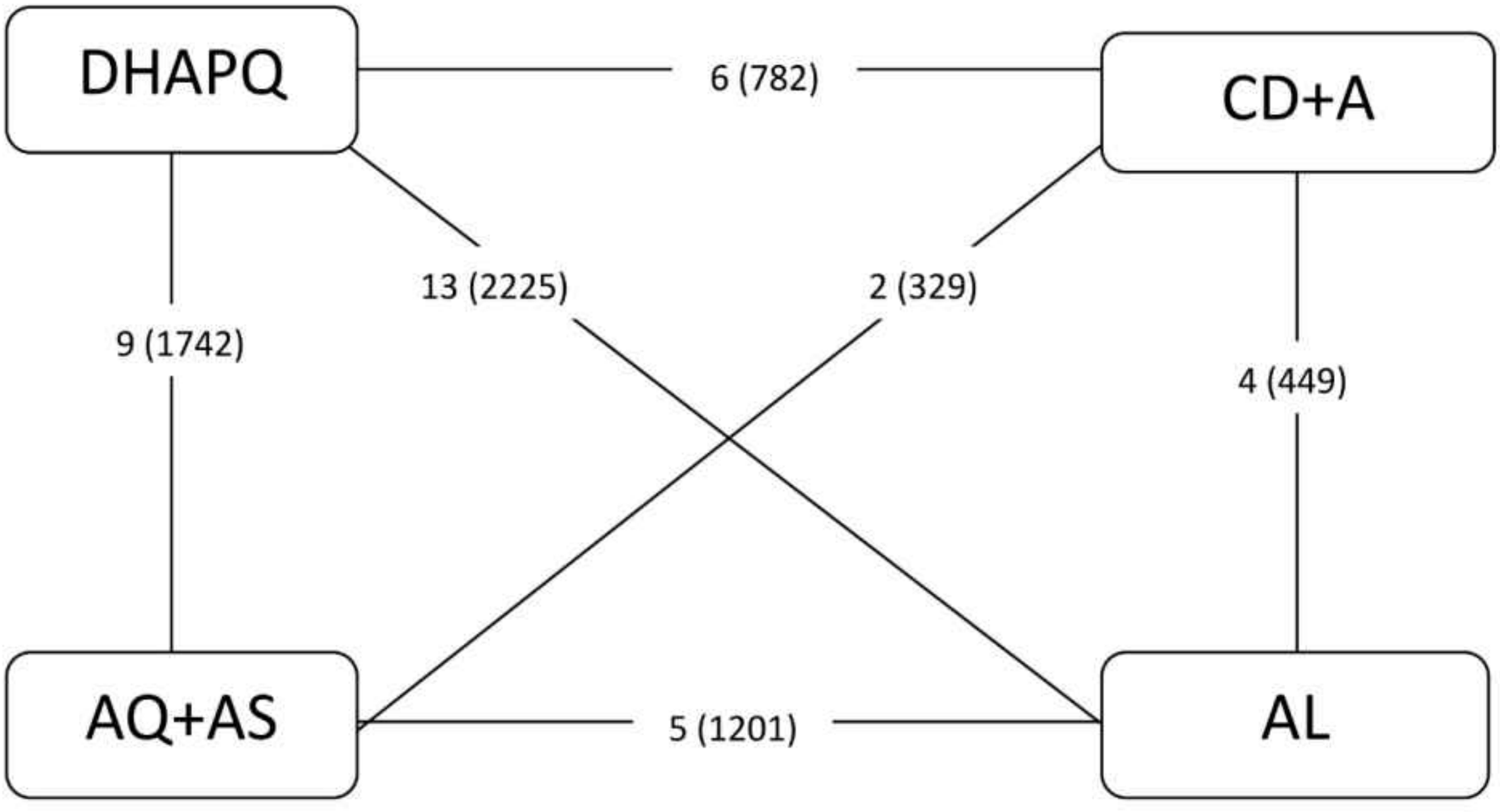
African site	Dihydroartemisinin-Piperaquine (DHAPQ)	Amodiaquine-Artesunate (AQ+AS)	Artemether-Lumefantrine (AL)	Chlorproguanil/ Dapsone-Artesunate (CD+A)	Mean age (years)
Manhica (after CD+A)	94/100	78/97			2.88
Mbarara (after CD+A)	63/65	59/70			2.43
Nanoro	187/219	199/290	115/292		2.24
Gabon	62/63	67/76	65/70		2.83
Afokang	67/72	78/83	84/87		2.94
Pamol	60/65	73/79	73/80		2.66
Ndola	67/67	63/69	63/75		2.45
Manhica (before CD+A)	78/82	70/86		42/84	2.82
Mbarara (before CD+A)	72/80	64/79		53/80	2.60
Rukara (after CD+A)	46/47		46/50		3.08
Jinja (after CD+A)	160/167		157/168		2.33
Tororo (after CD+A)	54/75		33/77		1.99
Mashesha (after CD+A)	49/52		51/52		2.90
Rukara (before CD+A)	22/23		18/21	4/23	2.71
Jinja (before CD+A)	37/39		35/38	34/40	2.62
Tororo (before CD+A)	109/141		88/138	71/142	2.11
Mashesha (before CD+A)	23/24		23/23	18/24	2.92

Network diagram



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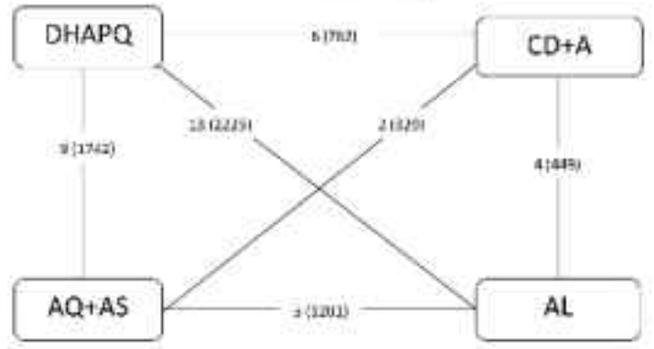
Network diagram



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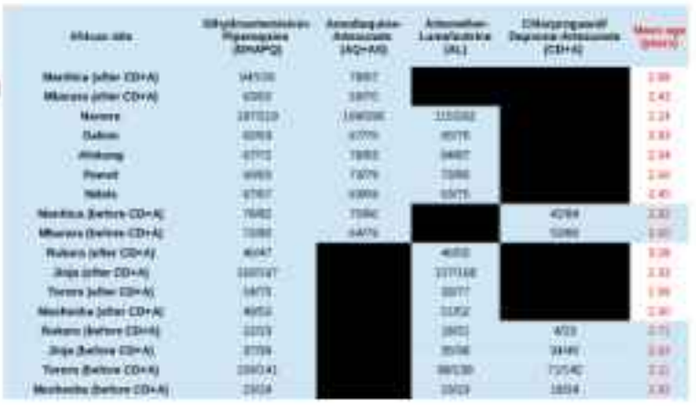

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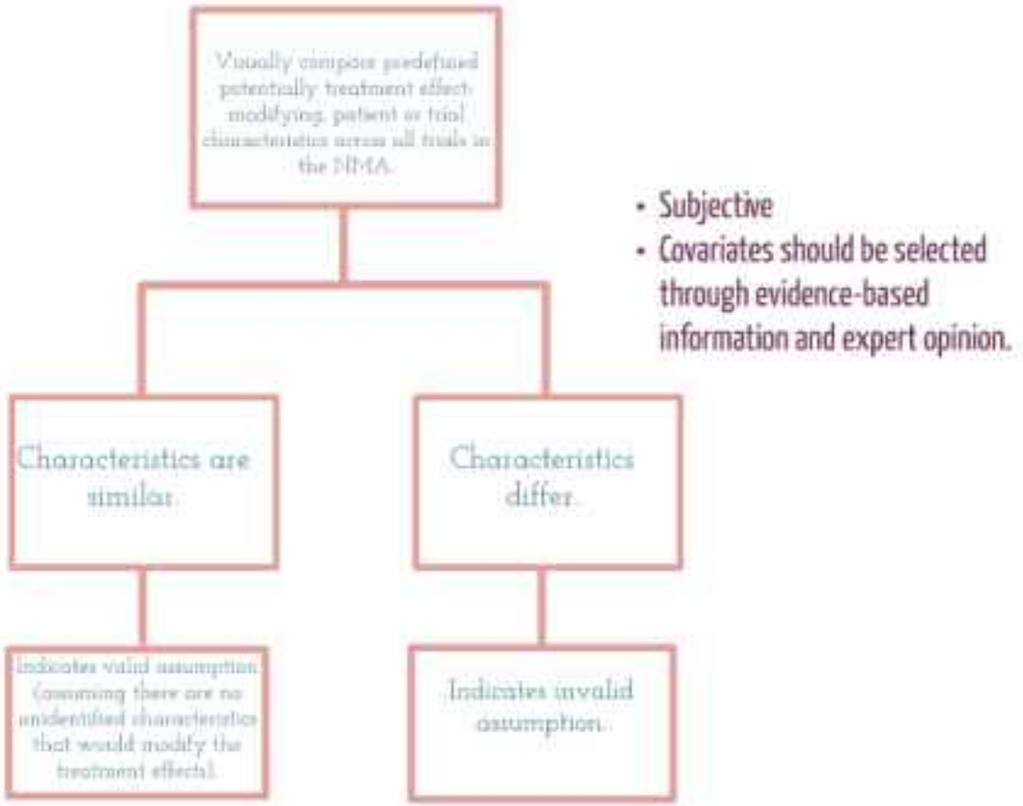

- Subjective
- Covariates should be selected through evidence-based information and expert opinion.

Visually compare predefined potentially treatment effect-modifying, patient or trial characteristics across all trials in the NMA.

- Subjective
- Covariates should be sele
  through evidence-based
  information and expert o

Characteristics are similar.

Characteristics differ.

Indicates valid assumption (assuming there are no unidentified characteristics that would modify the treatment effects).

Indicates invalid assumption.

Method C1: Comparing patient or trial characteristics

Patient-level characteristics are similar across sites

Site	Country	Male n (%)	Weight (kg) mean (SD)	Temp. (°C) mean (SD)	Current fever1 n (%)	Gametocytes present n (%)	Age (years), mean (SD)	Log parasite density/µL mean (SD)	CQR	SPR	Transmission rate	Location
Afokang	Nigeria	129 (49.4)	12.9 (3.4)	37.9 (1.3)	155 (59.4)	11 (4.2)	2.94 (1.28)	9.83 (1.21)	0.45	0.30	0.50	West
Gabon	Gabon	97 (42.9)	12.3 (2.8)	37.8 (1.2)	114 (50.4)	10 (4.4)	2.83 (1.28)	9.99 (1.45)	1.00	0.23	0.50	West
Jinja (after)	Uganda	177 (47.6)	11.2 (3.0)	38.0 (1.1)	253 (68.0)	13 (3.5)	2.33 (1.17)	10.56 (0.93)	0.28	0.49	0.26	East/South
Jinja (before)	Uganda	67 (54.0)	11.7 (3.0)	37.8 (1.1)	74 (59.7)	12 (9.7)	2.62 (1.19)	10.27 (1.07)	0.28	0.49	0.26	East/South
Manhiça (after)	Mozambique	61 (53.5)	12.1 (3.0)	38.1 (1.4)	75 (65.8)	0 (0)	2.88 (1.30)	10.56 (1.01)	0.78	0.22	0.47	East/South
Manhiça (before)	Mozambique	229 (57.1)	12.4 (2.6)	38.2 (1.3)	283 (70.6)	2 (0.5)	2.82 (1.00)	10.59 (1.09)	0.78	0.22	0.47	East/South
Mashesha (after)	Rwanda	50 (47.6)	11.8 (2.2)	38.3 (1.5)	64 (61.0)	0 (0)	2.90 (1.05)	10.24 (1.46)	0.50	0.12	0.50	East/South
Mashesha (before)	Rwanda	43 (60.6)	12.0 (2.1)	38.6 (1.3)	55 (77.5)	18 (25.4)	2.92 (1.09)	10.38 (1.19)	0.50	0.12	0.50	East/South
Mbarara (after)	Uganda	66 (44.6)	11.3 (2.6)	37.7 (1.1)	81 (54.7)	44 (29.7)	2.43 (1.07)	10.09 (1.31)	0.81	0.61	0.19	East/South
Mbarara (before)	Uganda	125 (48.8)	11.7 (2.5)	38.0 (1.1)	167 (65.2)	57 (22.3)	2.60 (1.10)	10.15 (1.29)	0.81	0.61	0.19	East/South
Nanoro	Burkina Faso	371 (45.8)	10.0 (2.6)	37.8 (1.3)	437 (54.0)	119 (14.7)	2.24 (1.18)	9.95 (1.17)	0.24	0.04	0.75	West
Ndola	Zambia	137 (55.9)	11.3 (2.7)	38.2 (1.3)	165 (67.3)	11 (4.5)	2.45 (1.20)	10.50 (1.13)	0.60	0.19	0.20	East/South
Pamol	Nigeria	115 (49.4)	12.5 (3.3)	37.9 (1.0)	158 (67.8)	22 (9.4)	2.66 (1.36)	9.80 (1.32)	0.45	0.30	0.50	West
Rukara (after)	Rwanda	48 (49.0)	12.2 (2.2)	38.1 (1.4)	64 (65.3)	7 (7.1)	3.08 (0.92)	10.02 (1.18)	0.40	0.36	0.30	East/South
Rukara (before)	Rwanda	38 (55.9)	11.2 (2.2)	38.7 (1.3)	56 (82.4)	1 (1.5)	2.71 (1.00)	9.60 (1.05)	0.40	0.36	0.30	East/South
Tororo (after)	Uganda	74 (47.4)	10.4 (2.1)	37.9 (1.2)	88 (56.4)	15 (9.6)	1.99 (0.99)	9.96 (1.10)	0.45	0.12	0.35	East/South
Tororo (before)	Uganda	212 (49.5)	10.6 (2.2)	37.5 (1.0)	188 (43.9)	90 (21.0)	2.11 (0.85)	9.75 (1.20)	0.45	0.12	0.35	East/South

Site-level characteristics differ across sites.
Such differences could certainly modify the treatment effects and violate the assumption.

Site	Country	Male n (%)	Weight (kg) mean (SD)	Temp. (°C) mean (SD)	Current fever1 n (%)	Gametocytes present n (%)	Age (years), mean (SD)	Log parasite density/μL mean (SD)	CQR	SPR	Transmission rate	Location
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