Learning from Systematic Review and Meta-analysis

Efficacy and Safety of Antiscabietic Agents: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials

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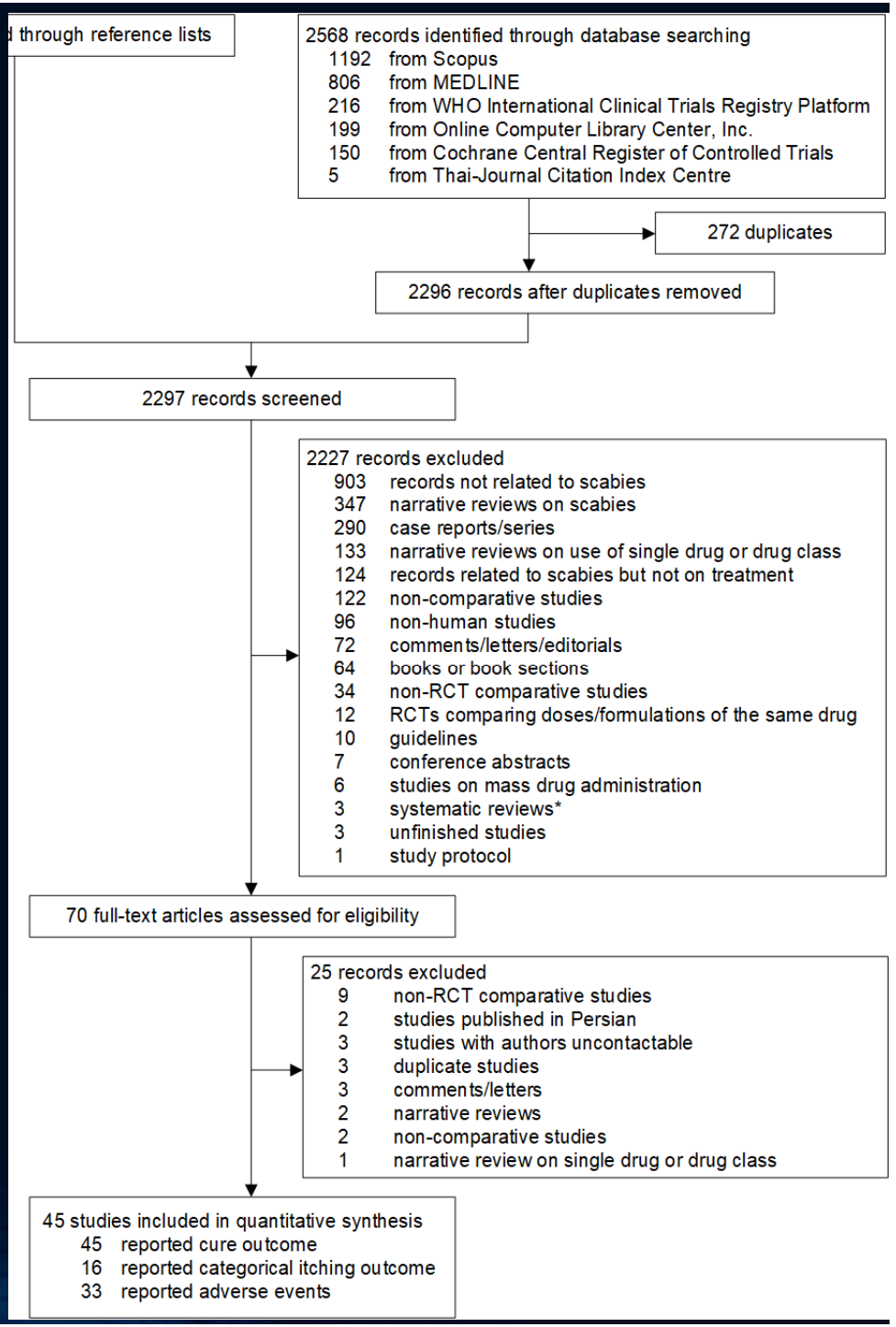
Outline

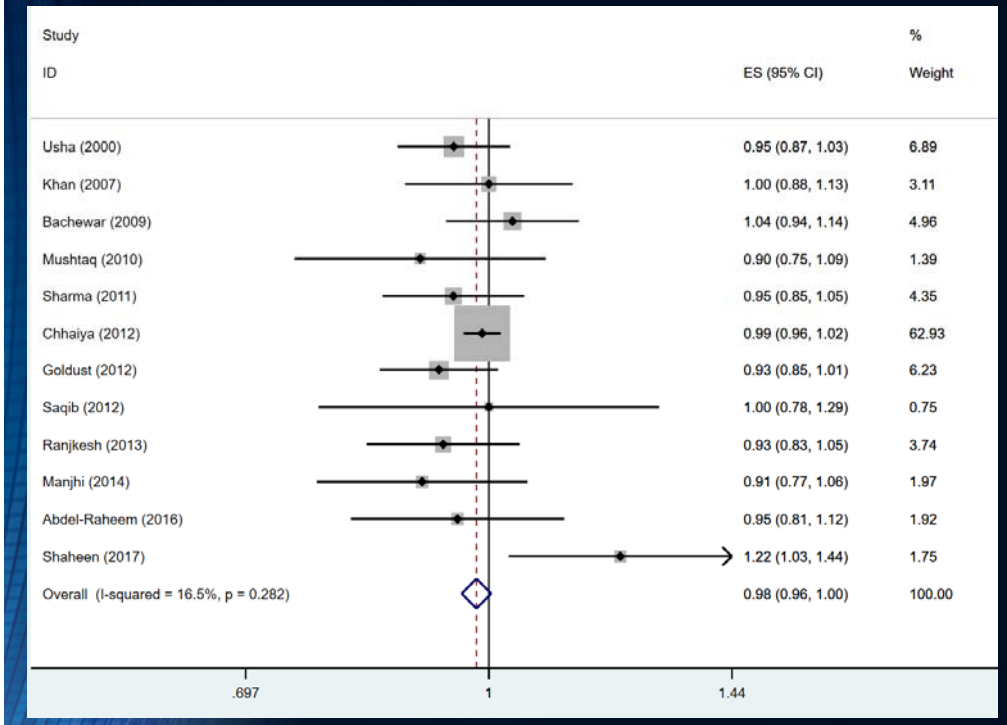
- Introduction to systematic review
- Introduction to network meta-analysis
- Systematic review and network meta-analysis of antiscabietic agents
  - Steps of conducting review
  - Problems and tips

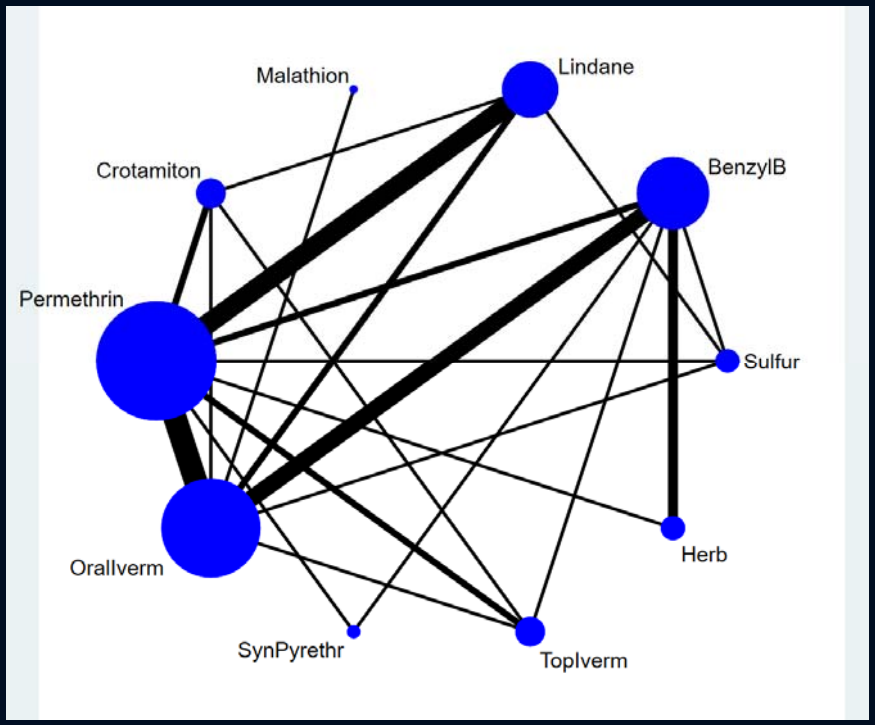
Systematic review

- A review conducted with a systematic approach in order to minimize bias and random error
- More complete, objective, transparent, and reproducible than traditional narrative reviews
- Allows quantitative synthesis of evidence using meta-analysis



Meta-analysis

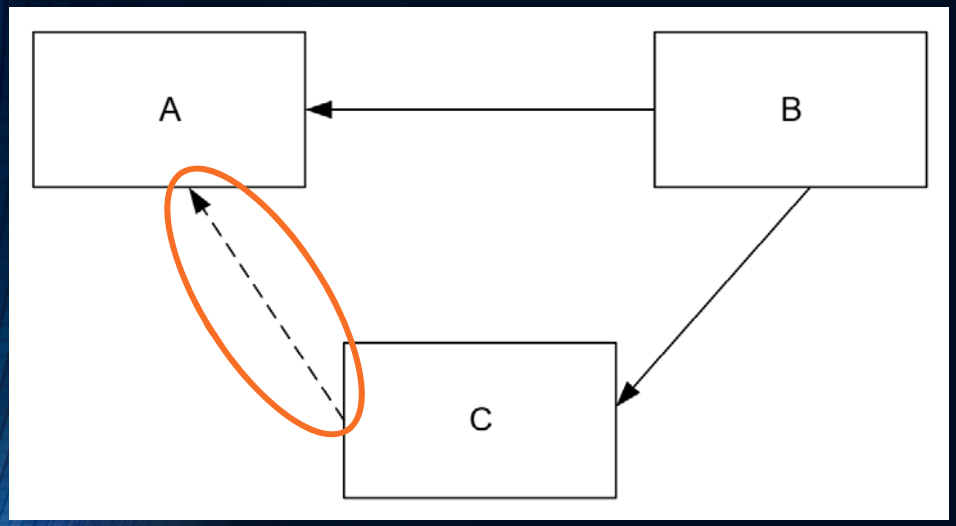




- Pairwise
- Direct

- Network
- Multiple treatment

Network meta-analysis



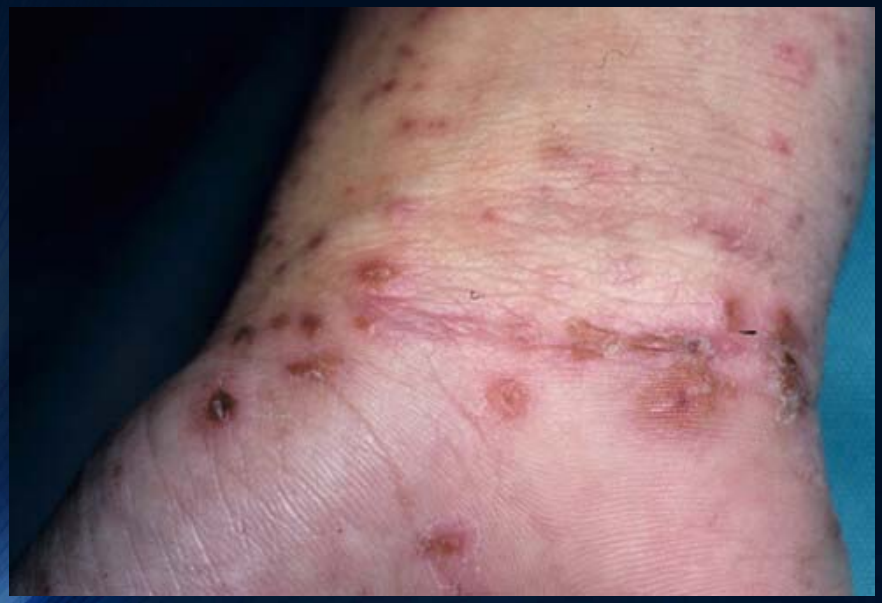
- > 2 groups of interest, > 1 comparison
- Advantages
  - Indirect comparisons
  - Ranking

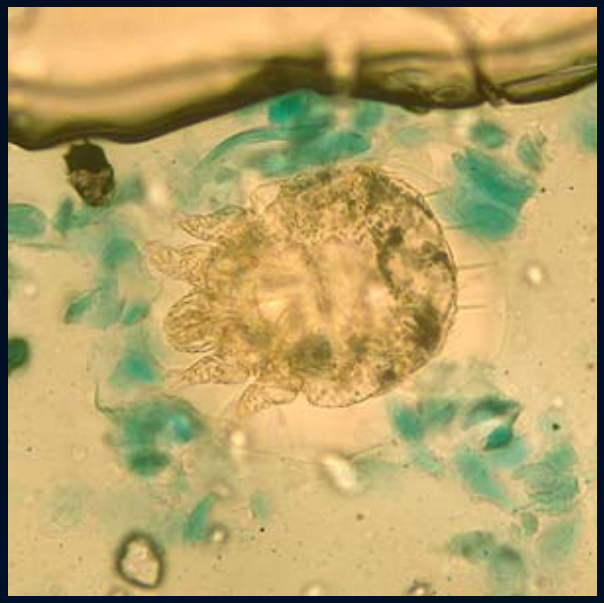
Efficacy and Safety of Antiscabietic Agents: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials

Why was this topic selected?

Why was this topic selected?

- Scabies: a common, highly contagious parasitic infestation of skin
  - Global prevalence ~ 100 million individuals
  - Prevalence 0.2% - 71.4% [Romani 2015]





Antiscabietic agents

Medication	Date introduced
Sulfur compounds	Centuries ago
Benzyl benzoate	1930s
Lindane	1940s
Malathion	1970s
Crotamiton	1970s
Permethrin	1980s
Oral ivermectin	1980s
Synergized pyrethrins	2000s
Topical ivermectin	2000s

Previous evidence

- 4 previous systematic reviews
  - Walker GJ, Johnstone PW. Interventions for treating scabies. Cochrane Database Syst Rev. 2000(3):Cd000320.
  - Strong M, Johnstone P. Interventions for treating scabies. Cochrane Database Syst Rev. 2007(3):Cd000320.
  - Johnstone P, Strong M. Scabies. BMJ Clin Evid. 2008;2008.
  - Dressler C, Rosumeck S, Sunderkötter C, Werner RN, Nast A. Originalarbeit: Therapie der Skabies: Systematische Literaturübersicht von randomisierten kontrollierten Studien. Deutsches Arzteblatt International. 2016;113(45):757-62.
- Standard pairwise meta-analysis on rates of treatment failure and itch persistence

Rationale

- From previous reviews
  - Some treatments have not been included in previous reviews, e.g., malathion, herbal medicine
  - Readers have been informed of the better treatment from each pairwise comparison, but not the best one among all available treatments
- Network meta-analysis has never been applied
  - Can indirectly compare all treatment options
  - Can demonstrate which treatment is the best among all available treatments

Research question

- Among all of the available treatments for scabies, which one is the most efficacious and has the lowest adverse events?
- PICO format
  - Patients: adults and children with scabies
  - Interventions, comparators: oral ivermectin, topical ivermectin, permethrin, sulfur, lindane, malathion, crotamiton, benzyl benzoate, synergized pyrethrins, herbal medicine, placebo, no treatment
  - Outcomes: clinical cure, microscopic cure, time to cure, persistent itching after treatment, adverse events

Goals of treatment

- Resolution of the skin lesions
- Eradication of scabietic mites
- Resolution of itching

Primary objectives

- To indirectly compare the RRs of achieving cure (clinical and/or microscopic) between treatments
- To estimate probability of being the best treatment in achieving cure, and rank the treatments according to their probability of being the best treatment in achieving cure

Secondary objectives

- To indirectly compare the RRs of having persistent itching by all treatments, estimate probability of being the best treatment in having lowest persistent itching, and rank the treatments according to their probability of being the best treatment in having lowest persistent itching
- To indirectly compare the RRs of having adverse events by all treatments, estimate probability of being the best treatment in having lowest adverse reactions, and rank the treatments according to their probability of being the best treatment in having lowest adverse reactions

Secondary objectives

- To simultaneously assess and rank the treatments according to their benefit in achieving cure and risk of having adverse drug reactions by probability of being the best treatment in each aspect

Registration at PROSPERO

UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for Health Research

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

Efficacy of antiscabietic agents: a systematic review and network meta-analysis of randomized controlled trials

Location of studies: Sources

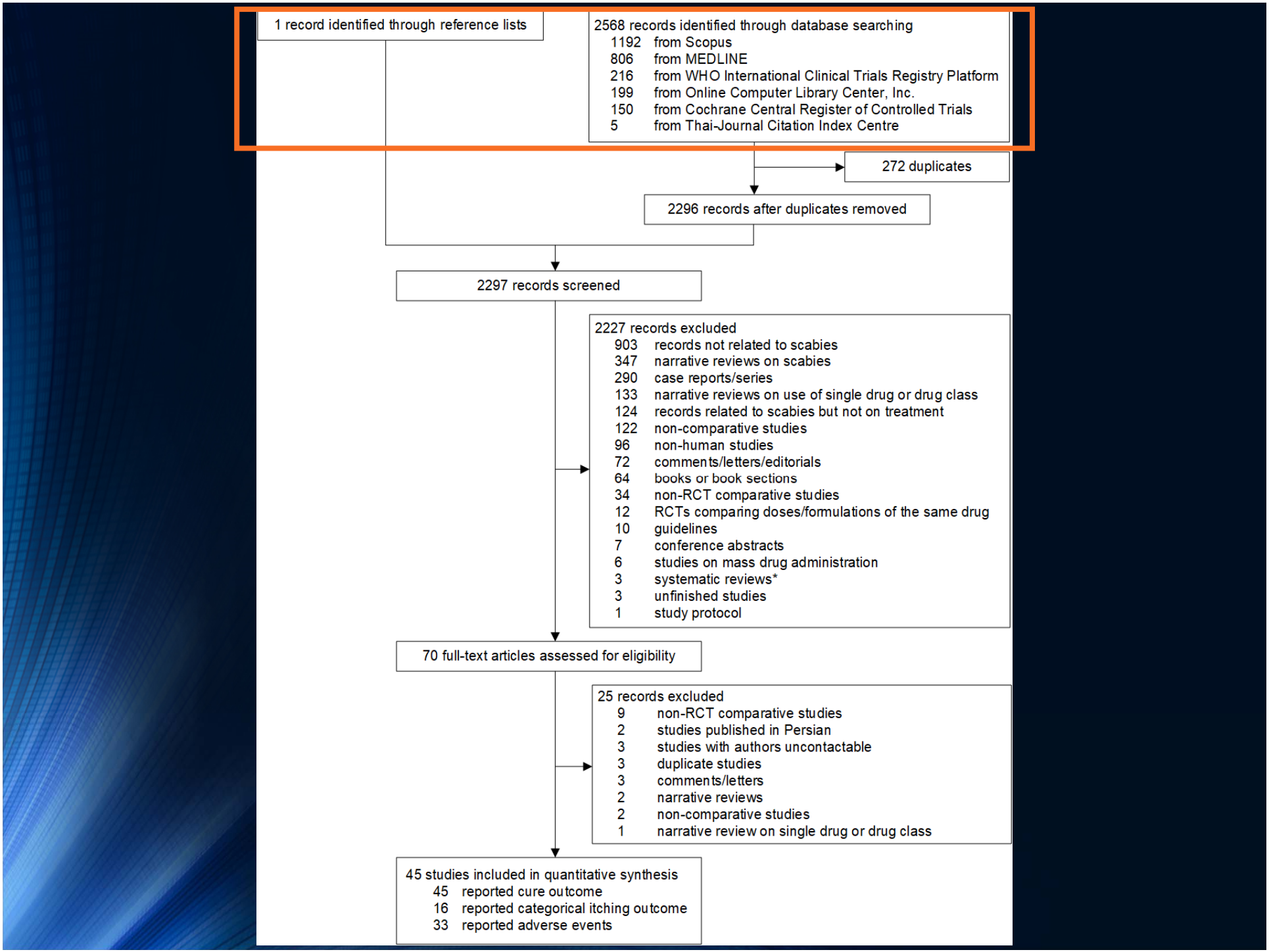
- Sources – literature search in an attempt to retrieve RCTs on treatment of scabies
  - MEDLINE via PubMed
  - Scopus
  - Cochrane Central Register of Controlled Trials
  - Thai-Journal Citation Index Centre
  - WHO International Clinical Trials Registry Platform for unpublished and ongoing studies
  - Online Computer Library Center, Inc. for theses and dissertations
  - References of previous systematic reviews

Location of studies: Search strategy

- MEDLINE via PubMed, Scopus
  - P: scabi*
  - I & C: sulfur, sulphur, "benzyl benzoate", lindane, "benzene hexachloride", hexachlorocyclohexane, malathion, malation, crotamiton, permethrin, ivermectin, pyrethr*, aloe*, plant*, herb*
  - O: -

Location of studies: Search strategy

- Cochrane Central Register of Controlled Trials
  - scabies
- Thai-Journal Citation Index Centre
  - scabies in article title, abstract, keywords
  - หิด in article title, abstract, keywords
- WHO International Clinical Trials Registry Platform
  - scabies
- Online Computer Library Center, Inc.
  - scabies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2568 records identified through database searching
1192 from Scopus
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272 duplicates
2296 records after duplicates removed
2297 records screened
2227 records excluded
903 records not related to scabies
347 narrative reviews on scabies
290 case reports/series
133 narrative reviews on use of single drug or drug class
124 records related to scabies but not on treatment
122 non-comparative studies
96 non-human studies
72 comments/letters/editorials
64 books or book sections
34 non-RCT comparative studies
12 RCTs comparing doses/formulations of the same drug
10 guidelines
7 conference abstracts
6 studies on mass drug administration
3 systematic reviews*
3 unfinished studies
1 study protocol
70 full-text articles assessed for eligibility
25 records excluded
9 non-RCT comparative studies
2 studies published in Persian
3 studies with authors uncontactable
3 duplicate studies
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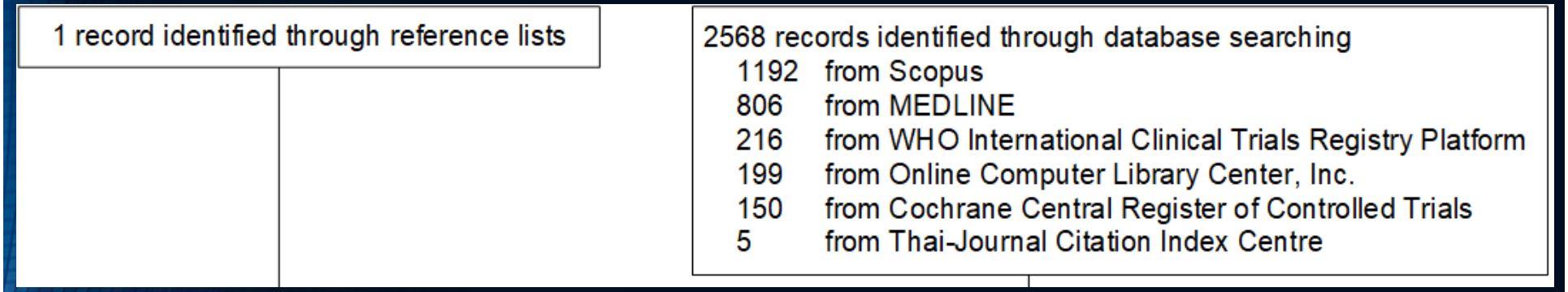
45 reported cure outcome
16 reported categorical itching outcome
33 reported adverse events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Selection of studies

- Screening by title and abstract
- Full text review for screened articles
- Articles selected based on inclusion and exclusion criteria

Selection of studies: Inclusion criteria

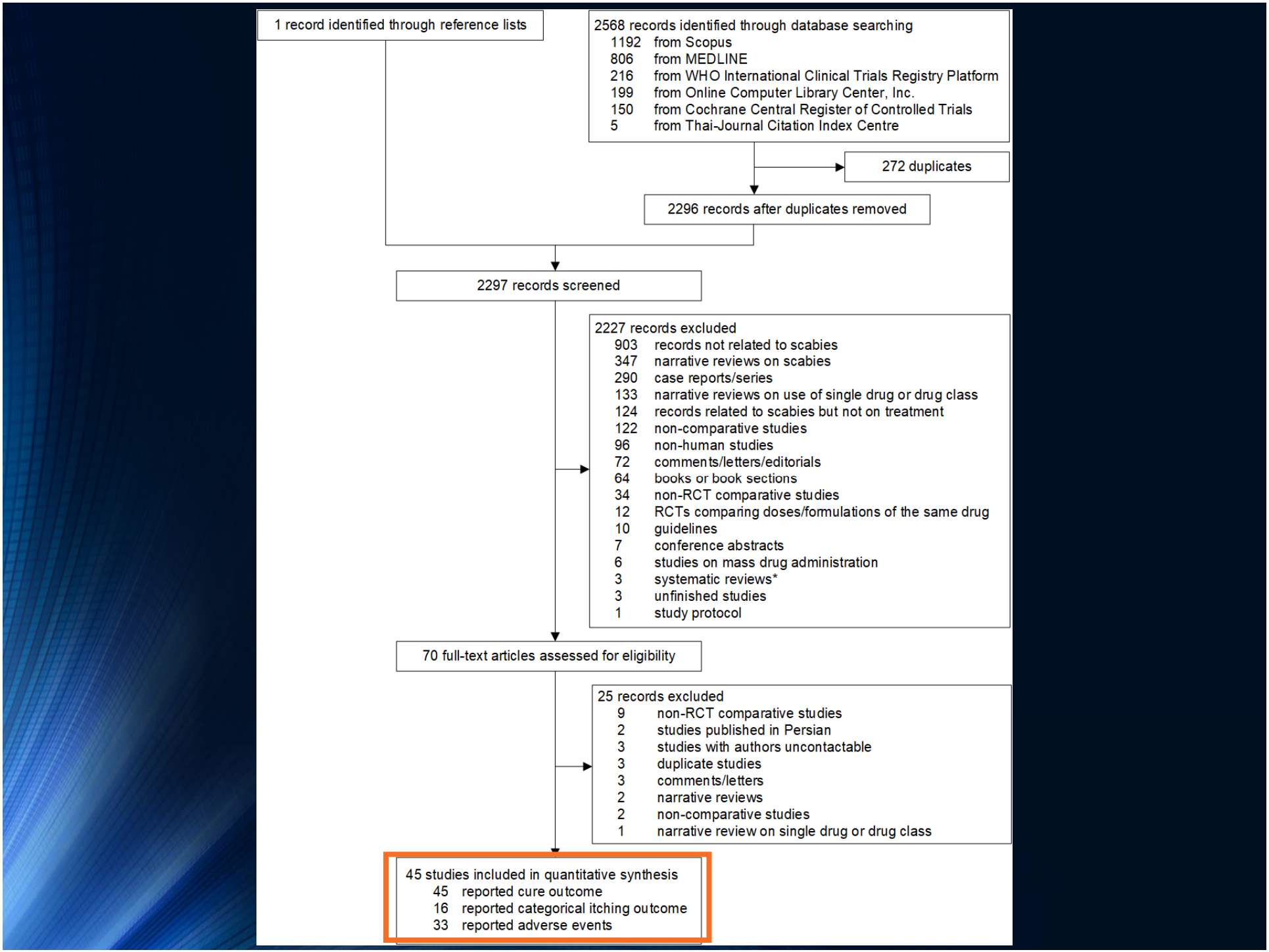
- Randomized controlled trial
- Either in adults or children with scabies
- Comparing any pair of the following:
  - Oral ivermectin
  - Topical ivermectin
  - Permethrin
  - Sulfur
  - Lindane
  - Malathion
  - Crotamiton
  - Benzyl benzoate
  - Aloe vera
  - Synergized pyrethrins
  - Herbal medicine
  - Placebo/No treatment

Selection of studies: Inclusion criteria (cont.)

- Reporting at least one of the following outcomes:
  - Cure
  - Time to cure
  - Persistent itching after treatment
  - Adverse events

Selection of studies: Exclusion criteria

- Exclusively comparing multiple regimens, doses, or formulations of the same drug
- Insufficient data for pooling after 3 attempts of contacting the author every 2 weeks
- Published in languages which the reviewers could not translate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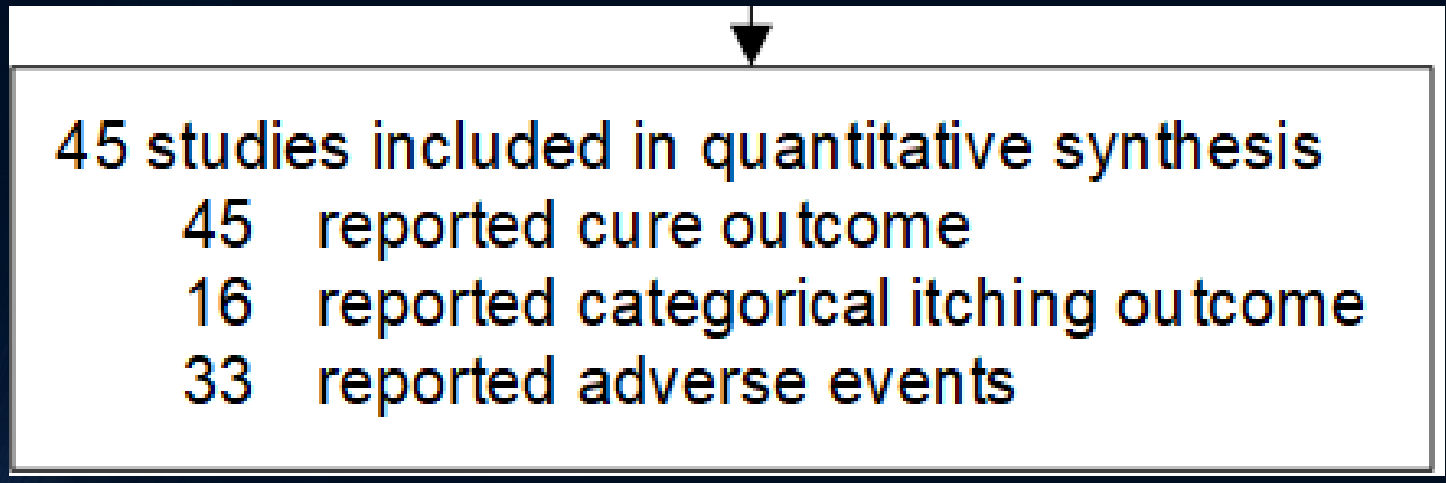
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Outcomes of interest

- Primary outcome: cure
  - Clinical cure: regression or resolution of pre-treatment skin lesions without new lesions as assessed on clinical examination of affected area(s) by investigators
  - Microscopic cure: negative microscopic examination (i.e., no mites, larvae, feces, or eggs found) by investigators of skin scraping from affected area(s) in an individual with previously positive microscopic examination (i.e., mites, larvae, feces, or eggs found)
  - Time to cure: reported time needed to achieve clinical and/or microscopic cure (e.g., in days) as assessed by investigators

Outcomes of interest (cont.)

- Secondary outcomes
  - Persistent itching after treatment: reported as either binary scale (presence/absence) or severity (e.g., in visual analog scale or Likert scale) as assessed by patients
  - Adverse drug reaction: reported as number/percentage of individuals experiencing any adverse event(s) after receiving the treatment as assessed by patients and/or investigators

Data extraction

- Performed independently by 2 reviewers
- Using data extraction form
- Disagreement was resolved by consensus with a supervisor

Data for pooling

Outcome	Treatment group	Yes	No	n	Incidence
59. Efficacy 1, at __ weeks	A				
	B				
	C				
	D				
60. Efficacy 2, at __ weeks	A				
	B				
	C				
	D				

Long format

study	treatment	d	n
1	A	9	140
1	C	23	140
1	D	10	138
2	B	11	78
2	C	12	85
2	D	29	170
3	A	79	702
3	B	77	694
4	A	18	671
4	B	21	535

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network setup d n, studyvar(study) trtvar(treatment)
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Wide format

study	dA	nA	dB	nB	dC	nC	dD	nD
1	9	140	.	.	23	140	10	138
2	.	.	11	78	12	85	29	170
3	79	702	77	694	.	.	.	.
4	18	671	21	535	.	.	.	.

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network setup d n, studyvar(study)
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Risk of bias assessment

- Performed independently by 2 reviewers
- Using the 6 domains and criteria as described in Cochrane Collaboration's tool for assessing risk of bias [Higgins 2011]
- Disagreement was resolved by consensus with a supervisor

Cochrane Collaboration's tool for assessing risk of bias

- Selection bias
  - Random sequence generation
  - Allocation concealment
- Performance bias
  - Blinding of participants and personnel
- Detection bias
  - Blinding of outcome assessment
- Attrition bias
  - Incomplete outcome data
- Reporting bias
  - Selective reporting
- Other bias
  - Other sources of bias

Cochrane Collaboration's tool for assessing risk of bias

Selection bias	• Random sequence generation • Allocation concealment
Performance bias	• Blinding of participants and personnel
Detection bias	• Blinding of outcome assessment
Attrition bias	• Incomplete outcome data
Reporting bias	• Selective reporting
Other bias	• Other sources of bias

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.

RANDOM SEQUENCE GENERATION

Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.

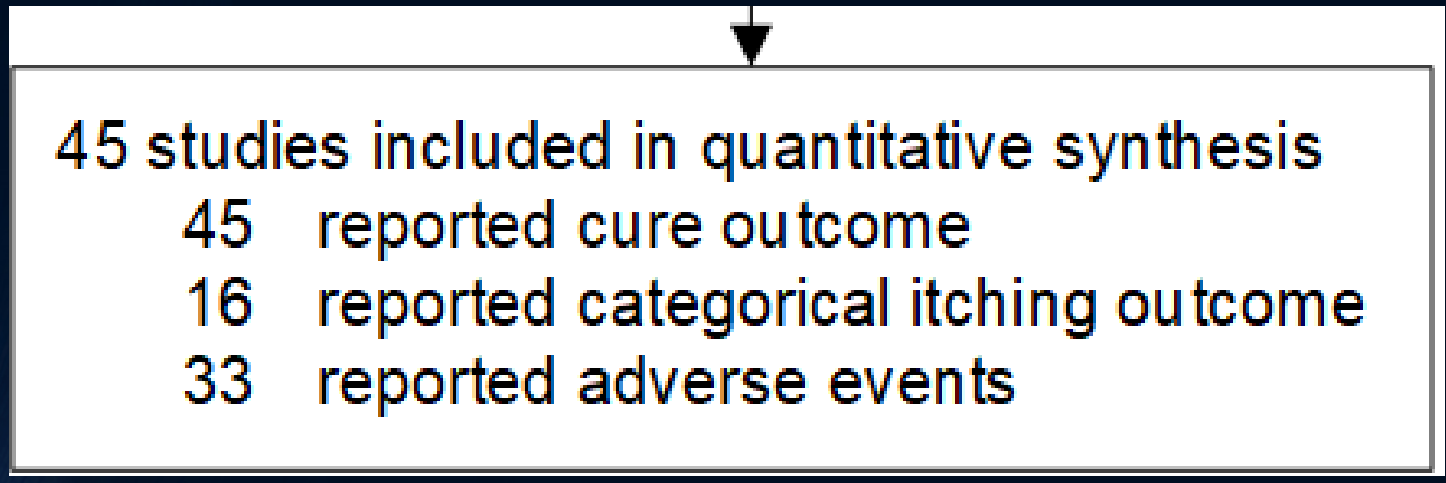
Criteria for a judgement of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.

[Higgins 2011]

http://handbook.cochrane.org/chapter_8/table_8_5_d_criteria_for_judging_risk_of_bias_in_the_risk_of.htm

RoB 1.0	RoB 2.0
Random sequence generation (*selection bias*)	Bias arising from the randomization process
Allocation concealment (*selection bias*)	
Blinding of participants and personnel (*performance bias*)	Bias due to deviations from intended interventions
Incomplete outcome data (*attrition bias*)	Bias due to missing outcome data
Blinding of outcome assessment (*detection bias*)	Bias in measurement of the outcome
Selective reporting (*reporting bias*)	Bias in selection of the reported result
Other bias	N/A
N/A	Overall bias

[Higgins 2016]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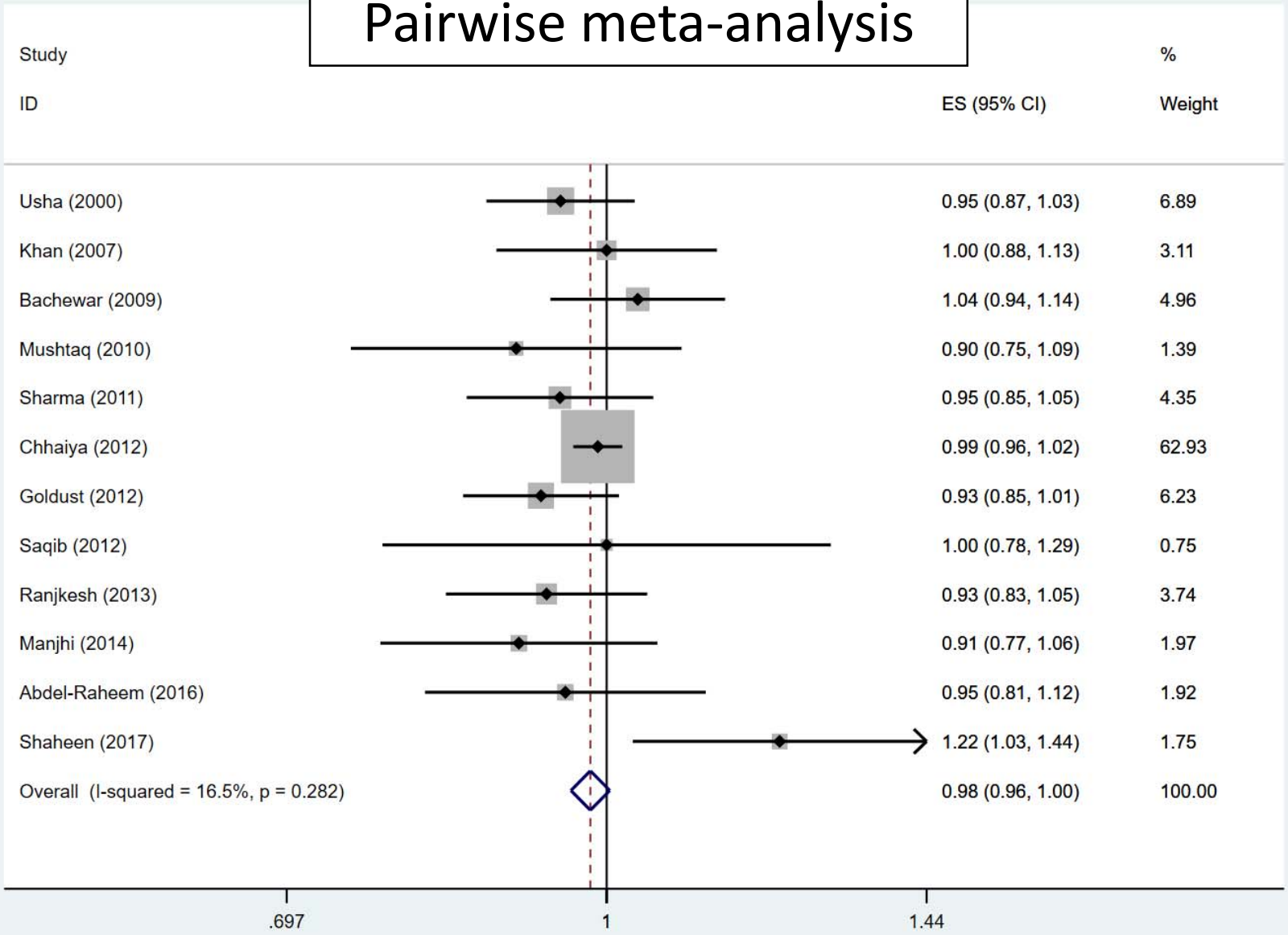
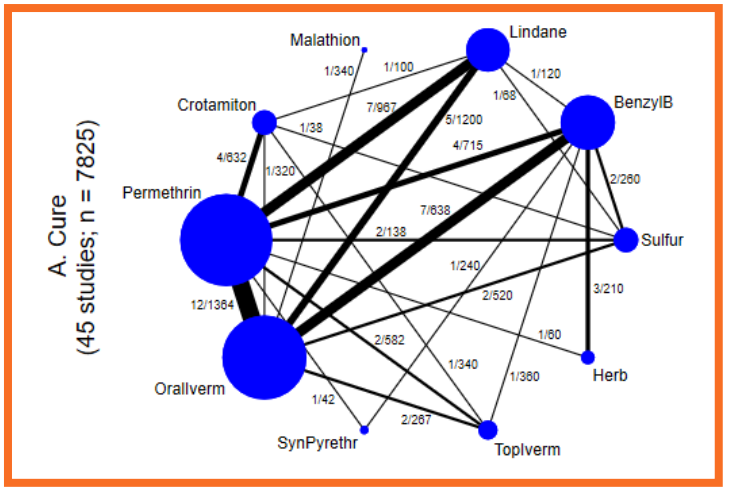
Pairwise meta-analysis

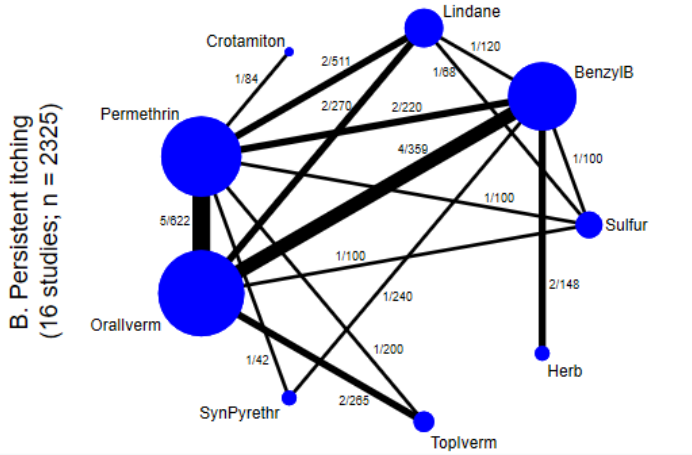


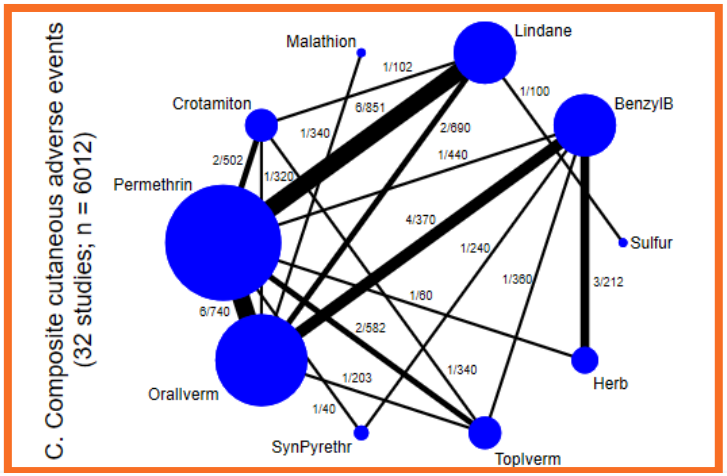
Network meta-analysis

- Treatments coded from old to new
  0. Placebo or no treatment
  1. Sulfur
  2. Benzyl benzoate
  3. Lindane
  4. Malathion
  5. Crotamiton
  6. Permethrin
  7. Oral ivermectin
  8. Synergized pyrethrins
  9. Topical ivermectin
  10. Herbal medicine

Reference treatment







Network meta-analysis

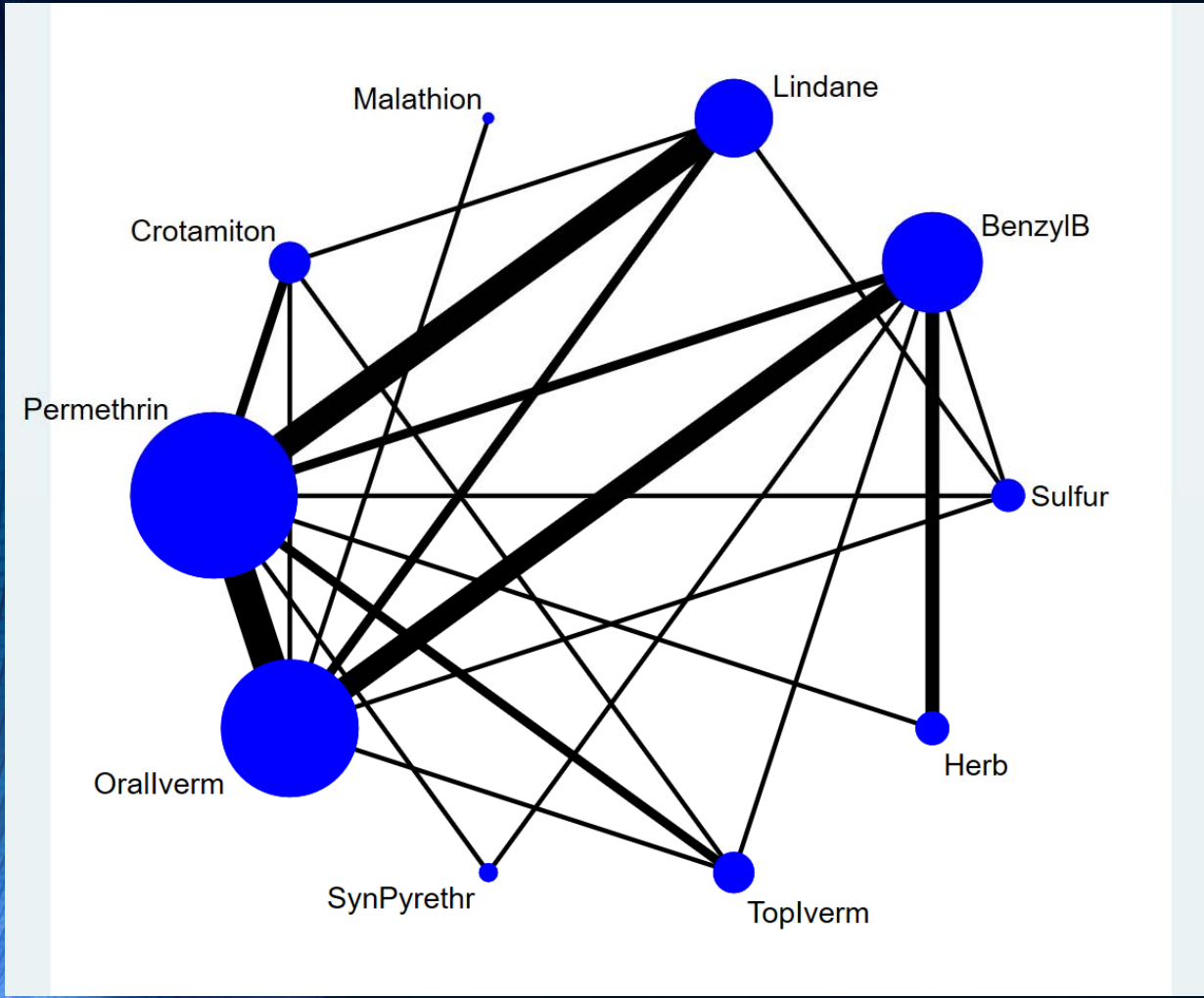
- Two-stage network meta-analysis applied
  1. Binary regression → ln(RR), variance-covariance
  2. Multivariate random effects meta-analysis with consistency model applied to pool ln(RR) across studies
- Multiple relative treatment comparisons based on network meta-analysis model
- Consistency assumption assessed by design-by-treatment interaction model

	Composite cutaneous adverse events									
Cure	Toplverm	**7.90 (2.06, 30.25)**	7.77 (0.97, 62.42)	1.82 (0.88, 3.77)	**2.58 (1.11, 5.96)**	**7.73 (1.77, 33.69)**	2.59 (0.99, 6.81)	1.82 (0.56, 5.89)	2.04 (0.91, 4.60)	0.96 (0.42, 2.18)
	1.05 (0.81, 1.35)	SynPyrethr	0.98 (0.10, 9.77)	**0.23 (0.07, 0.77)**	0.33 (0.09, 1.20)	0.98 (0.16, 5.81)	0.33 (0.08, 1.29)	0.23 (0.05, 1.03)	0.26 (0.06, 1.03)	**0.12 (0.04, 0.40)**
	1.38 (1.12, 1.70)	**1.31 (1.01, 1.72)**	Sulfur	0.23 (0.03, 1.67)	0.33 (0.04, 2.44)	0.99 (0.10, 10.28)	0.33 (0.05, 2.11)	0.23 (0.03, 2.09)	0.26 (0.03, 2.10)	**0.12 (0.02, 0.97)**
	0.99 (0.86, 1.13)	0.94 (0.76, 1.17)	**0.72 (0.60, 0.85)**	Permethrin	1.42 (0.78, 2.58)	**4.25 (1.10, 16.39)**	1.42 (0.72, 2.82)	1.00 (0.38, 2.65)	1.12 (0.54, 2.35)	0.53 (0.26, 1.05)
	1.02 (0.88, 1.17)	0.97 (0.77, 1.21)	**0.74 (0.62, 0.87)**	1.03 (0.95, 1.11)	Orallverm	3.00 (0.89, 10.06)	1.01 (0.47, 2.17)	0.71 (0.23, 2.16)	0.79 (0.36, 1.74)	**0.37 (0.17, 0.83)**
	1.40 (0.99, 1.98)	1.34 (0.91, 1.97)	1.02 (0.71, 1.46)	**1.42 (1.02, 1.96)**	**1.38 (1.01, 1.89)**	Malathion	0.34 (0.08, 1.40)	0.24 (0.05, 1.22)	0.26 (0.06, 1.12)	**0.12 (0.03, 0.53)**
	1.27 (1.08, 1.50)	1.22 (0.96, 1.54)	0.93 (0.77, 1.11)	**1.29 (1.16, 1.43)**	**1.25 (1.13, 1.40)**	0.91 (0.65, 1.27)	Lindane	0.70 (0.22, 2.28)	0.79 (0.31, 2.04)	**0.37 (0.15, 0.93)**
	1.17 (0.92, 1.48)	1.12 (0.84, 1.48)	0.85 (0.66, 1.09)	1.18 (0.96, 1.45)	1.15 (0.93, 1.42)	0.83 (0.57, 1.22)	0.92 (0.73, 1.15)	Herb	1.12 (0.34, 3.72)	0.53 (0.18, 1.53)
	1.29 (1.08, 1.53)	1.23 (0.95, 1.59)	0.94 (0.76, 1.16)	**1.30 (1.13, 1.50)**	**1.27 (1.10, 1.47)**	0.92 (0.65, 1.30)	1.01 (0.86, 1.19)	1.10 (0.86, 1.41)	Crotamiton	0.47 (0.19, 1.18)
	1.16 (0.99, 1.35)	1.10 (0.89, 1.37)	0.84 (0.70, 1.00)	**1.17 (1.04, 1.31)**	**1.14 (1.02, 1.28)**	0.83 (0.59, 1.15)	0.91 (0.79, 1.05)	0.99 (0.82, 1.19)	0.90 (0.76, 1.07)	BenzylB

Consistency assessed by design-by-treatment interaction model

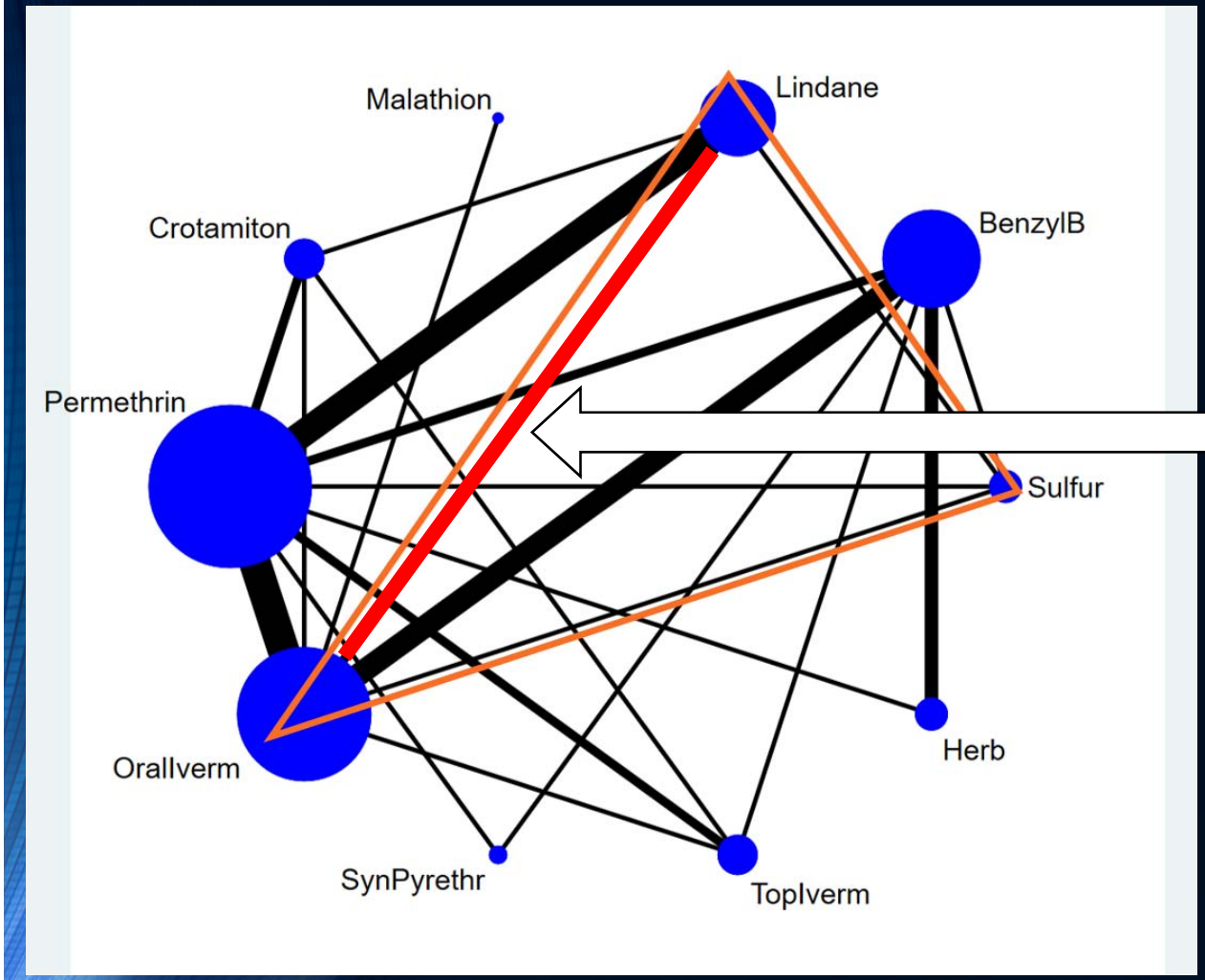
- Cure: χ^2=10.83, df=24, *P*=0.990
- Cutaneous AEs: χ^2=37.82, df=14, *P*<0.001

Cutaneous AEs



33 studies

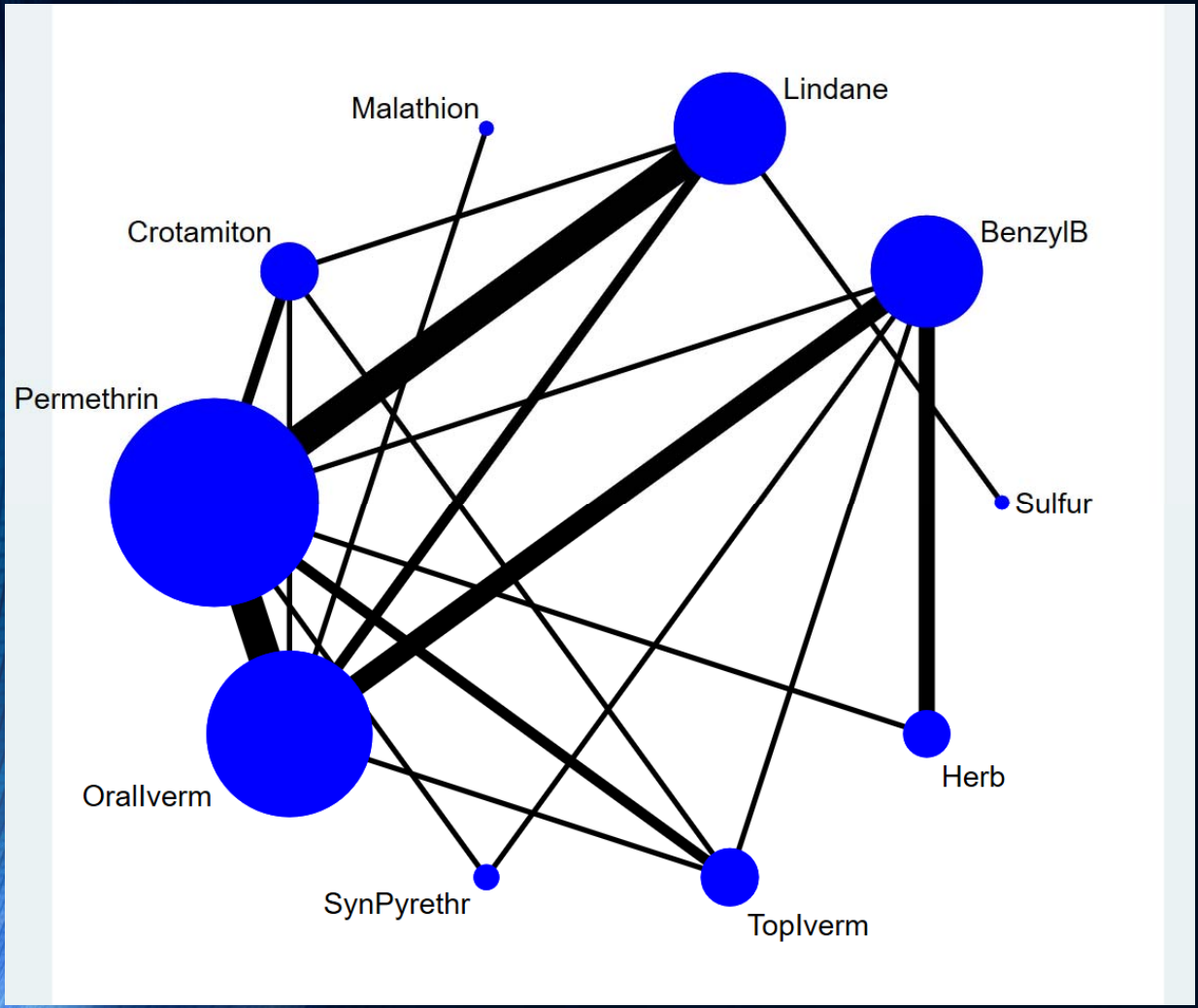
Cutaneous AEs



33 studies

- Inconsistency factor = 6.029 (2.82, 9.24)
- 4 studies in loop explored
- 1 study with outcomes assessed at 2 weeks (Cf. 4 weeks in other 3 studies) excluded

Cutaneous AEs



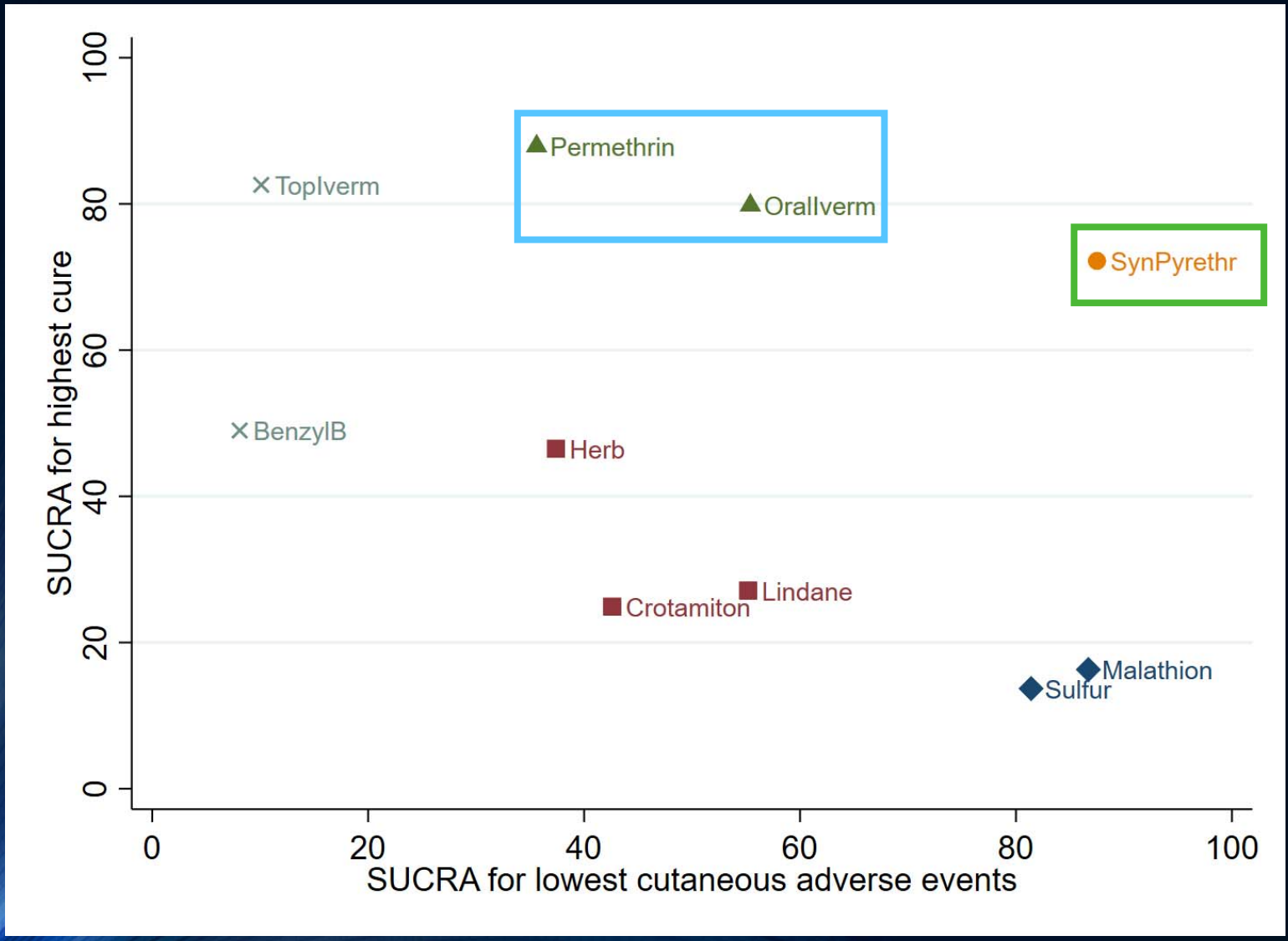
32 studies

Design-by-treatment interaction model: χ^2=17.14, df=11, *P*=0.104

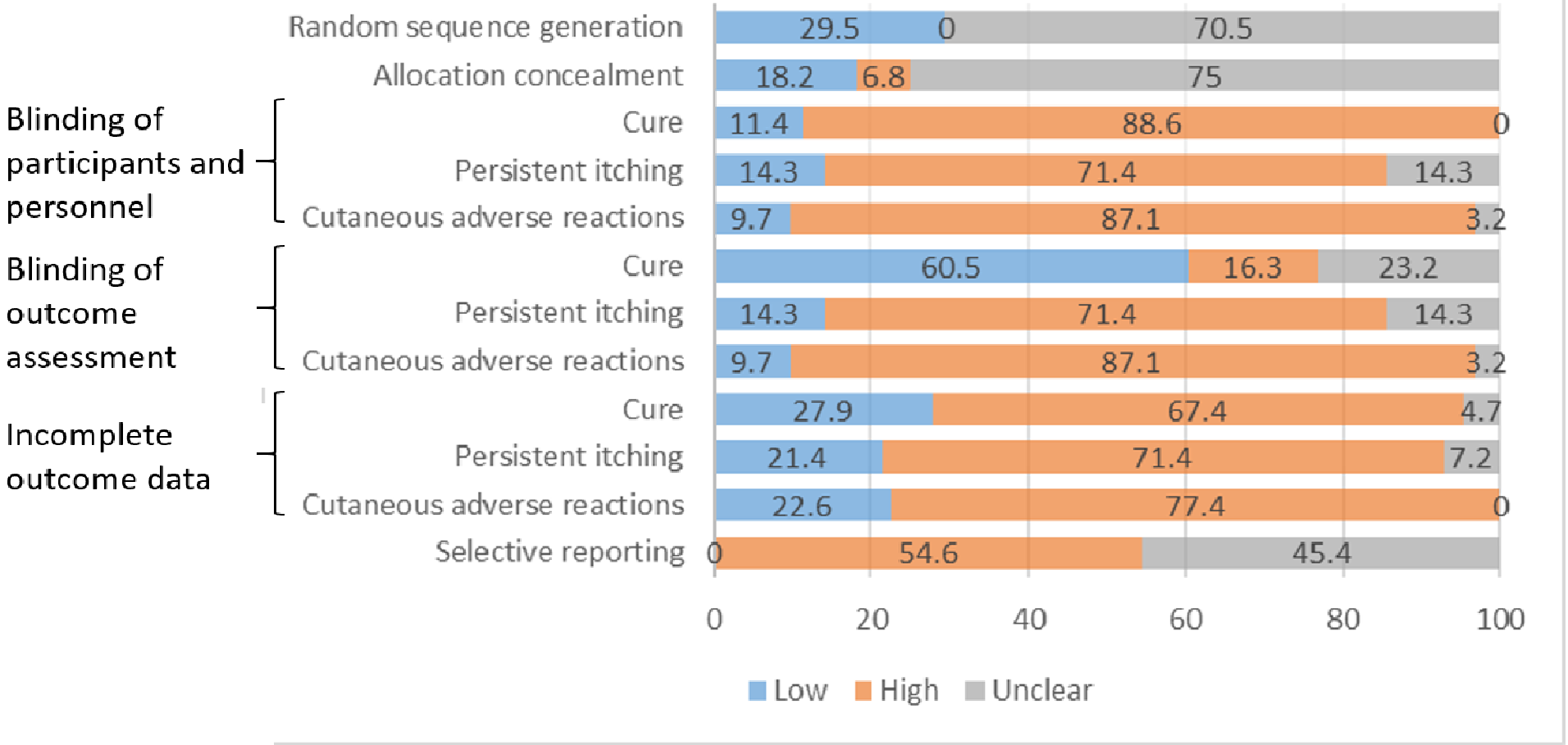
Treatment ranking by SUCRA

Rank	Cure; treatment (SUCRA)	Cutaneous AEs; treatment (SUCRA)
1	Permethrin (87.9)	SynPyrethr (87.5)
2	TopIverm (82.6)	Malathion (86.7)
3	OralIverm (79.8)	Sulfur (81.4)
4	SynPyrethr (72.2)	OralIverm (55.4)
5	BenzylB (49)	Lindane (55.2)
6	Herb (46.5)	Crotamiton (42.6)
7	Lindane (27.1)	Herb (37.4)
8	Crotamiton (24.9)	Permethrin (35.6)
9	Malathion (16.3)	TopIverm (10.1)
10	Sulfur (13.7)	BenzylB (8.1)

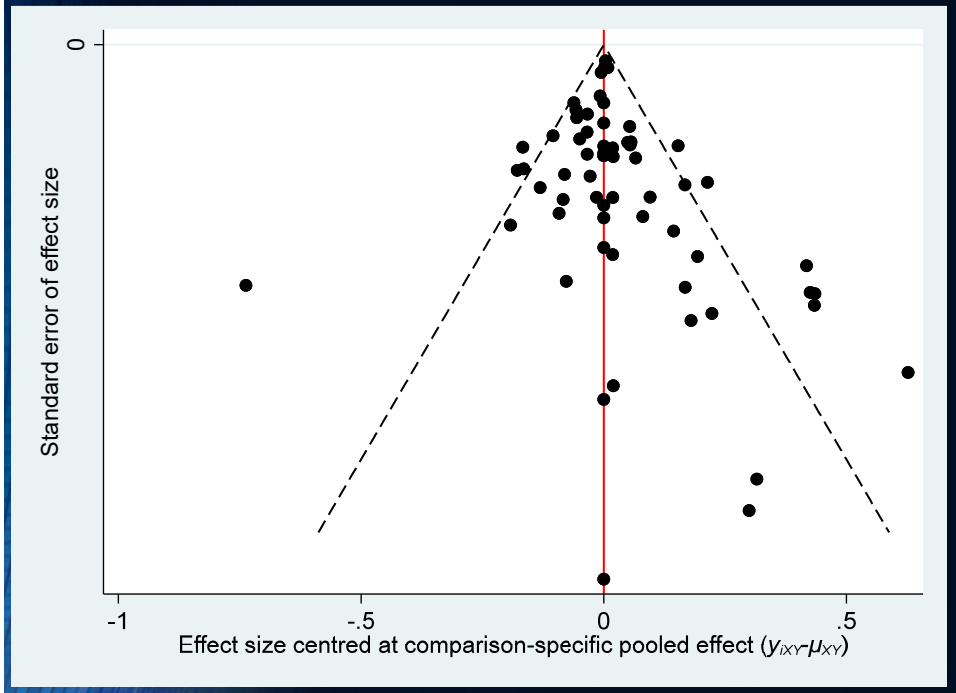
Clustered ranking plot



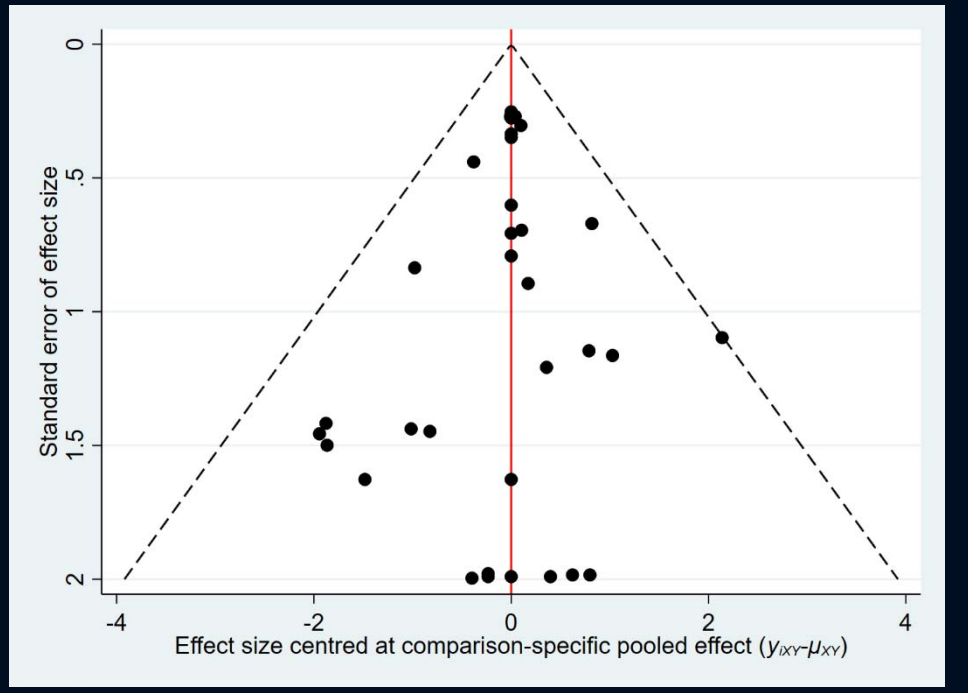
Risk of bias


Random sequence generation
Allocation concealment
Blinding of participants and personnel
Cure
Persistent itching
Cutaneous adverse reactions
Blinding of outcome assessment
Cure
Persistent itching
Cutaneous adverse reactions
Incomplete outcome data
Cure
Persistent itching
Cutaneous adverse reactions
Selective reporting
29.5
0
70.5
18.2
6.8
75
11.4
88.6
0
14.3
71.4
14.3
9.7
87.1
3.2
60.5
16.3
23.2
14.3
71.4
14.3
9.7
87.1
3.2
27.9
67.4
4.7
21.4
71.4
7.2
22.6
77.4
0
0
54.6
45.4
0
20
40
60
80
100
Low
High
Unclear

Comparison-adjusted funnel plots



Cure



Cutaneous AEs

Conclusion

- Synergized pyrethrins – most balanced
- No one treatment was the best in all aspect
- Physicians can choose one with good cure and acceptable adverse reactions

PRISMA checklist for network meta-analysis [Hutton 2015]

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review	

PRISMA checklist [Moher 2009]

Table 1. Checklist of items to include when reporting a systematic review or meta-analysis.

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	

References

- Higgins J, Altman D, Sterne J. Assessing risk of bias in included studies. 2011. In: Cochrane Handbook for Systematic Reviews of Interventions Version 510 (updated March 2011). The Cochrane Collaboration.
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- Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and MetaAnalyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.
- Romani L, Steer AC, Whitfeld MJ , Kaldor JM. Prevalence of scabies and impetigo worldwide: A systematic review. Lancet Infect Dis 2015;15:960-7

Thank you for your kind attention