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► **To cite this version:**

Valentin Navel, Aurélien Mulliez, Cédric Benoist d'Azy, Julien Steven Baker, Jean Malecaze, et al.. Efficacy of treatments for Demodex blepharitis: A systematic review and meta-analysis. *The Ocular Surface*, 2019, 17 (4), pp.655-669. 10.1016/j.jtos.2019.06.004 . hal-02971873

HAL Id: hal-02971873

<https://hal.science/hal-02971873>

Submitted on 21 Jul 2022

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1 **Efficacy of treatments for Demodex blepharitis:**

2 **a systematic review and meta-analysis**

3
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22
23 **Financial disclosures:** none reported

24 **Running title:** Therapeutics evaluation in Demodex blepharitis

25 **Word count** for text only (not including abstract, acknowledgment, references, and citations
26 of references within the text): 3030

27 **Abstract**

28 **Purpose:** We conducted a systematic review and meta-analysis to evaluate the efficacy of
29 different treatment for Demodex blepharitis. Parameters studied were mites count,
30 improvement of symptoms and mites' eradication, stratified on type of treatments and mode
31 of delivery of treatments (local or systemic).

32 **Method:** The PubMed, Cochrane Library, Embase, ClinicalTrials.gov, Google scholar and
33 Science Direct databases were searched for studies reporting an efficacy of treatments for
34 Demodex blepharitis.

35 **Results:** We included 19 studies (14 observational and 5 randomized clinical trials), for a total
36 of 934 patients, 1741 eyes, and 13 different treatments. For mites count, eradication rate, and
37 symptoms improvement, meta-analysis included fifteen, fourteen and thirteen studies,
38 respectively. The overall effect sizes for efficiency of all treatments, globally, were 1.68
39 (95CI 1.25 to 2.12), 0.45 (0.26 to 0.64), and 0.76 (0.59 to 0.90), respectively. Except usual lid
40 hygiene for mites count, Children's Hospital of Eastern Ontario ointment (CHEO) for both
41 eradication rate and symptoms, and CHEO, 2% metronidazole ointment, and systemic
42 metronidazole for symptoms, all treatments were efficient. Stratified meta-analysis did not
43 show significant differences between local and systemic treatments (1.22, 0.83 to 1.60 vs
44 2.24, 1.30 to 3.18 for mites count; 0.37, 0.21 to 0.54 vs 0.56, 0.06 to 0.99 for eradication rate;
45 and 0.77, 0.58 to 0.92 vs 0.67, 0.25 to 0.98 for symptoms improvement).

46 **Conclusion:** We reported the efficiency of the different treatments of Demodex blepharitis.
47 Because of less systemic side effects, local treatments seem promising molecules in the
48 treatment of Demodex blepharitis.

49

50 **Keywords:** Demodex – Blepharitis – Infection – Immunology – Inflammation – Tea tree oil –
51 Ivermectin – Pilocarpine – Metronidazole

52 **Introduction**

53 Blepharitis is a common eye inflammation affecting eyelash, eyelid and ocular surface with
54 sometimes corneal resounding. Among many causes, Demodex mites are found since the 19th
55 century with princep observation by Henle and Simon [1,2]. There are two host-specific
56 obligate mites' species found in human being's hair follicles, sebaceous glands (Zeiss
57 'glands) and eyelid glands (Meibum's glands) causing anterior and posterior blepharitis:
58 Demodex follicularum and Demodex brevis. Typically, Demodex follicularum found in
59 clusters around the eyelash and eyelid skin whereas Demodex brevis resided alone in the deep
60 of sebaceous and Meibomian glands [3–5]. Mites' presence may cause inflammatory process
61 in some eyelid tissues, however the pathogenesis' role of Demodex in inflammatory process
62 of blepharitis is discussed. Demodex would be the vector for number of bacterial and mycotic
63 pathogens, resulting in an immunological response at the eyelid margins, with redness, itching
64 and burning sensations [6–8]. Diagnosis of Demodex blepharitis is classically obtained by
65 parasitologist with skin or follicles biopsies [1–6,8,9] or more recently by confocal
66 microscopy [10,11]. Cylindrical dandruff at the base of eyelash is considered as
67 pathognomonic of Demodex infestation [5,12,13].

68 This physiological lack of knowledge and saprophyte presence of Demodex in healthy eyes
69 have an impact on therapeutics with very few studies in international scientific literature.
70 During long years, usual lid hygiene has been used to treat this kind of resistant blepharitis,
71 sometimes with sulphuric ointment [1], yellow mercuric ointment [1,4,9,14], pilocarpine gel
72 [15,16] or locals' antibiotics [17] without proof of efficacy. Anthelminthics, with systemic
73 side effects, have been used empirically these last years [18–21]. New local therapy based on
74 tea tree oil (TTO) and terpinen-4-ol (T4O) have been tested recently [18,21–32], opening a
75 new therapeutic field. To our knowledge, there are no synthesis of literature comparing

76 Demodex treatments. To allow a future consensus or new treatment elaboration is of major
77 interest.

78 Therefore, we aimed to compute a systematic review and meta-analysis to compare all
79 efficacy of Demodex blepharitis treatments. More specifically, we aimed assess the
80 comparative efficiency of local and systemic treatments and to evaluate influencing
81 parameters in therapeutic efficacy.

82

83 **Methods**

84 **Literature search**

85 We have searched all articles in PubMed, The Cochrane Library, Central, Embase,
86 ClinicalTrial.gov, Google Scholar and ScienceDirect databases from February 2018 to August
87 2018 with following keywords: (blepharitis OR blepharitides) AND (drug* OR
88 pharmacotherapy OR therap* OR treat* OR administration OR patient* OR outcome* OR
89 efficacy OR effective* OR clinical OR management OR compliance OR adherence). We
90 limited our search to articles written in English, French, or Spanish. No minimal sample size
91 was applied. To be included, articles needed to evaluate a therapy concerning Demodex
92 blepharitis proved by parasitological examination or confocal microscopy or cylindrical
93 dandruff. We imposed no limitation of regional origin or control group nature. In addition,
94 references list of all publications was manually searched to identify any other ones not found
95 with electronic search. The search strategy is presented in Figure 1. One author conducted all
96 literature searches (Valentin Navel) and collated the abstracts. Two authors (Valentin Navel
97 and Cédric Benoist d’Azy) separately reviewed the abstracts and based on the selection
98 criteria, decided the suitability of the articles for inclusion. A third author (Frédéric Dutheil)
99 was asked to review the articles where consensus on suitability was debated. Finally, all
100 authors reviewed eligible articles.

101 **Quality of assessment**

102 Although not created for that, the “Strengthening the Reporting of Observational studies in
103 Epidemiology” (STROBE) criteria may be inappropriately used as an assessment tool to
104 judge study quality, as well as the CONSORT guidelines for randomized clinical trials.
105 STROBE and CONSORT are checklists of 22 and 30 items, respectively. We attributed one
106 point per items, then converted into percentage to give a quality score for each included study
107 [33–36].

108 We also used the SIGN criteria to also judge observational studies and randomized clinical
109 trials, with the dedicated evaluation grids. SIGN Cohort Studies and SIGN Controlled Trials
110 statements are a checklist of 18 and 14 items, respectively. We gave a general quality score
111 for each include study based on the main causes of bias evaluated in section 1 of both
112 checklists through 4 possibilities of answers (yes, no, can’t say or not applicable) [37].

113

114 **Statistical considerations**

115 Statistical analyses were performed using Stata (v12, StataCorp, US) [38–44]. Parameters
116 were reported as mean \pm standard-deviation (SD) or number (%) for continuous or categorical
117 variables. Treatment efficacy was assessed using Hedges bias corrected effect size (ES) of
118 parasite count evolution (before-after treatment) as primary outcome. Parasite eradication rate
119 and symptoms improvement rate were considered as secondary outcome. ES and 95%
120 confidence interval (CI) were presented on forest plots, as a unitless measure of the effects of
121 treatments for Demodex blepharitis on mites count, eradication rate, and symptoms
122 improvement. An ES centered at zero means the absence of efficacy, 0.2 a small effect, 0.5 a
123 moderate effect, and 0.8 a large effect [45]. Funnel plots assessed the publication bias. I-
124 squared (I^2) quantified heterogeneity between studies, graded as low (<25%), moderate (25-
125 50%) or high (>50%). All statistical tests were two-sided; significance was set for $p < 0.05$.

126 When sample size was sufficient, meta-regressions (expressed as regression coefficient and
127 95% CI) were proposed to study relationships between parameters variation and clinically
128 relevant parameters such as age, sex ratio and eyelash sampling method.

129

130 **Results**

131 With the keywords described, an initial search produced 2796 articles (Fig 1). After removal
132 of the duplicates and applying selection criteria, we included 19 articles [14–16,18,18–32].

133

134 More details on study characteristics, quality of articles (Figures 2 and 3), method of
135 Demodex identification, type of treatments, protocol for each treatment, inclusion and
136 exclusion criteria of each included study, population, aims and outcomes of included studies
137 are described in Appendix 1.

138

139 **Meta-analyses and meta-regressions**

140 *Mites count:* Fifteen studies were included [14,16,19–25,27–32] with an overall ES of 1.68
141 (95CI 1.25 to 2.12) for all treatments. Except usual lid hygiene, all treatments decreased mites
142 count (Fig 4 and Fig 5, and Appendix 2). Stratified meta-analysis did not show significant
143 differences between local (1.22, 0.83 to 1.60) and systemic (2.24, 1.30 to 3.18) treatments
144 (Fig 6 and 7), or between eyelash sampling with (1.31, 0.80 to 1.81) or without (1.49, 1.02 to
145 1.96) cylindrical dandruff (Fig 6, and Appendix 5). There were also no significant influences
146 of age and gender (Fig 6). Meta-regressions comparing treatments efficacy were not feasible
147 due to limited number of data (most treatments were only reported in one study), despite
148 stratified meta-analysis on each treatment demonstrated ES greater than 2.5 for oral
149 metronidazole + oral ivermectin (3.66, 95CI 2.84 to 4.48), and 5%TTO (2.66, 2.17 to 3.15);
150 greater than 1 for ivermectin alone (1.80, 1.10 to 2.50), 50%TTO (1.74, 0.81 to 2.67),

151 pilocarpine gel (1.72, 0.71 to 2.73), and T4O (1.36, 0.60 to 2.11); and greater than 0.8 for
152 Cilclar 1.9% + oxide mercuric ointment + ether application (0.81, 0.26 to 1.34), CHEO (0.53,
153 0.12 to 0.94) and OLSP (0.95, 0.53 to 1.37) (Fig 4 and 5, and Appendix 2).

154 ***Eradication rate of mites:*** Fourteen studies were included [14,15,18,20–24,27,29–32,46] with
155 an overall ES of 0.45 (0.26 to 0.64) for all treatments. Except CHEO, 2% metronidazole
156 ointment, and systemic metronidazole, all treatments improved eradication rate (Fig 4 and 5,
157 and Appendix 3). Stratified meta-analysis did not show significant differences between local
158 (0.37, 0.21 to 0.54) and systemic (0.56, 0.06 to 0.99) treatments (Fig 6 and 7), or between
159 eyelash sampling with (0.30, 0.12 to 0.51) or without (0.46, 0.25 to 0.68) cylindrical dandruff
160 (Fig 6, and Appendix 5). As for mites count, there were also no significant influences of age
161 and gender (Fig 6), and meta-regressions comparing treatments efficacy were also not feasible
162 due to limited number of data (one study per treatment, mainly). However, stratified meta-
163 analysis on each treatment demonstrated ES greater than 0.8 for systemic metronidazole +
164 ivermectin (1.00, 0.80 to 1.00), and pilocarpine gel (0.92, 0.81 to 0.97); greater than 0.5 for
165 Cilclar 1.9% + oxide mercuric ointment + ether application (0.57, 0.33 to 0.59), 50%TTO
166 (0.54, 0.25 to 0.82), and ivermectin (0.54, 0.01 to 1.00); and greater than 0.2 for Ocusoft lid
167 scrub (0.46, 0.28 to 0.65), 5%TTO (0.43, 0.04 to 0.87), T4O (0.41, 0.23 to 0.61), and usual lid
168 hygiene (0.22, 0.02 to 0.53) (Fig 4 and 5, and Appendix 3).

169 ***Symptoms improvement:*** Thirteen studies were included [14–16,18,19,21–24,26,28,31,32,46]
170 with an overall ES of 0.76 (0.59 to 0.90) for all treatments. Except CHEO, all treatments
171 improved symptoms (Fig 4 and 5, and Appendix 4). Stratified meta-analysis did not show
172 significant differences between local (0.77, 0.58 to 0.92) and systemic (0.67, 0.25 to 0.98)
173 treatments (Fig 6 and 7), or between eyelash sampling with (0.81, 0.37 to 1.00) or without
174 (0.73, 0.55 to 0.89) cylindrical dandruff (Fig 6, and Appendix 5). As for mites count and
175 eradication rate, there were also no significant influences of age and gender (Fig 6), and meta-

176 regressions comparing treatments efficacy were also not feasible due to limited number of
177 data (one study per treatment, mainly). CHEO were less efficient than usual lid hygiene with
178 a coefficient of -1.02 (-1.33 to -0.71) (Fig 6). However, stratified meta-analysis on each
179 treatment demonstrated ES greater than 0.8 for T4O (1.00, 0.85 to 1.00), Ocusoft lid scrub
180 (1.00, 0.86 to 1.00), 50% TTO (0.97, 0.86 to 1.00) and 5% TTO (0.81, 0.60 to 0.96); greater
181 than 0.5 for Cilclar 1.9% + oxide mercuric ointment + ether application (0.79, 0.52 to 0.92),
182 systemic ivermectin (0.78, 0.31 to 1.00), 4% pilocarpine gel (0.74, 0.60 to 0.84) and usual lid
183 hygiene (0.54, 0.42 to 0.65); and greater than 0.2 for Naviblef (0.41, 0.26 to 0.57), 2%
184 metronidazole ointment (0.20, 0.04 to 0.62) and systemic metronidazole (0.20, 0.04 to 0.62)
185 (Fig 4 and 5, and Appendix 4).

186

187 **Discussion**

188 Our study is the first systematic evaluation of treatments for Demodex blepharitis.
189 Physiopathology of this commensal parasite were a hindrance to the development of various
190 therapies. We reported the efficiency of the different treatments of Demodex blepharitis.
191 More interestingly, stratified meta-analysis did not show significant differences between local
192 and systemic treatments. Because of less side effects, local treatments seem promising to
193 manage Demodex blepharitis. We did not demonstrate influence of sociodemographic in the
194 efficacy of treatments.

195

196 **Rational of study**

197 Despite Demodex was first identified 150 years ago, it only attracted wider interest recently,
198 over the last 10 years [1]. In fact, the relative current ignorance of physiopathology is a
199 drawback in therapeutics' evaluations. Initially, Demodex was considered as a saprophyte
200 parasite normally colonising the eyelashes. Current consensus proposed to consider as

201 physiological a number of mites <5 mites/cm² for skin lesions or <3 mites at the root of each
202 eyelash [4,20,47]. However, mites outbreaks may play a role in the pathophysiology of the
203 infection, causing a local inflammatory reaction and a repercussion on the ocular surface
204 [1,5,8,9,13,48–50]. Therefore, several therapeutics were used such as antiparasitic,
205 antiseptics, or anti-inflammatory drugs. Our meta-analysis was needed because most
206 treatments were used without sound proof of efficiency and without randomized controlled
207 trials comparing efficiency of treatments. We chose Demodex count as primary judgement
208 criteria because the presence of some mites may be considered as normal and outbreaks
209 pathological. Eradication rate was chosen as a secondary judgement criteria to evaluate the in
210 vivo killing effect in parallel of mites count decrease.

211

212 **Interest molecules**

213 Initially, usual lid hygiene has been used to treat resistant blepharitis with sulphuric ointment
214 [1], yellow mercuric ointment [1,4,9,14] or pilocarpine gel [15,16]. Sulphuric ointment or
215 yellow mercury treatments were poorly supported and are now obsolete (last publications are
216 more than twenty years old) [2,5,13,51,52] whereas pilocarpine, a well-known molecule in
217 glaucoma, showed interesting results with gel form [15,16]. Its antiparasitic effect may be
218 based on parasympathomimetic action resulting in paralysis of mites' respiration and mobility
219 [15,16]. Over the last three decades, anthelmintics, such as ivermectin or metronidazole,
220 were used empirically to treat Demodex blepharitis, as an off-label drug prescription outside
221 marketing authorisation [18–21]. Ivermectin is an effective orally administered antiparasitic
222 drug, known since several years. Whereas the acaricidal effect of metronidazole on the
223 Demodex mite is unknown [20,53,54], the parasitic killing effect of ivermectin is well known,
224 through a selective activity against glutamate-gated chloride ion channels from the peripheral
225 nervous system of invertebrates. These last years, news locals' therapies based on TTO and

226 T4O have been tested [18,21–32], opening a new therapeutic field. TTO is a natural substance
227 extracted from the leaves of the *Melaleuca alternifolia*, a plant of the Myrtaceae family. This
228 product was known for a long time by Australian indigenous concerning antiseptic properties
229 [55,56]. Some studies concerning TTO proved its antifungal, antibacterial, antiviral and
230 antiparasitological effects [57–61]. T4O is the most active ingredient of TTO with
231 concentration from 30 to 48% [56]. The results of TTO, T4O and pilocarpine uses
232 corroborated the results of in vitro killing effect [27]. To our knowledge, in most countries, no
233 treatment based on TTO or T4O are available to clinicians with marketing authorisation to
234 treat *Demodex* blepharitis. It would be interesting to evaluate these news locals' treatments in
235 clinical trials to prove their efficacy, and to consider these molecules in therapeutic
236 association.

237

238 **Proposal of recommendations for the treatment of *Demodex* blepharitis**

239 In our meta-analysis, all *Demodex* blepharitis included from individual studies were resistant
240 to the first-line treatment such as usual lid hygiene and local antibiotics [14–16,18–32,46].
241 Thus, negative results of usual lid hygiene were expected. However, its mechanical effects
242 have been proved and should at an early stage [17,62–64]. More interestingly, we
243 demonstrated that local and systemic treatments had comparable efficiency (1.22, 0.83 to 1.60
244 vs 2.24, 1.30 to 3.18 for mites count; 0.37, 0.21 to 0.54 vs 0.56, 0.06 to 0.99 for eradication
245 rate; and 0.77, 0.58 to 0.92 vs 0.67, 0.25 to 0.98 for symptoms improvement). As mentioned
246 upper, *Demodex* mites are present in healthy eyelids so it could be unnecessary to employ
247 toxic or very effective systemic treatment. In included studies, clinical side effects or hepatic
248 toxicity were not observed with systemic ivermectin or metronidazole [18,19,21]. However,
249 hypersensitivity reaction is more common with systemic treatments compared with local
250 treatments. Serious reactions were observed using ivermectin or metronidazole in other

251 parasitic infections such as Mazzotti reaction (tachycardia, hypotension, arthralgias, oedema,
252 and abdominal pain), Steven-Johnson and Lyell disease, fatal encephalopathy, increased INR
253 (International Normalized Ratio) with hemorrhage, decrease in leukocyte count and anemia,
254 hepatitis, elevation of liver enzymes, and elevation of bilirubin. Ivermectin should not be used
255 during pregnancy since safety in pregnancy has not been established [20,21,53,54]. In
256 blepharitis Demodex, the sides effects with local uses of TTO, T4O or pilocarpine were rare
257 and benign, such as eyes irritations, redness eyelid, cutaneous eczema, itching or burning
258 sensations, but never systemic reactions [14,18,22–32,46]. Therefore, considering that
259 cylindrical dandruffs at the base of the eyelashes are pathognomonic of Demodex blepharitis
260 [5,13,27], and considering our results, we propose to treat blepharitis with cylindrical
261 dandruffs with antiparasitic local first-line treatment i.e. the association of TTO, T4O or
262 pilocarpine gel with usual lid hygiene once or twice daily during 1 to 3 months. In second-line
263 or in severe cases, systemic treatment such as ivermectin or metronidazole could be added,
264 which may also decrease recurrence – although not proved –, without severe side effects
265 reported with systemic low dose in the treatment of Demodex blepharitis. Severe cases refer
266 to severe ocular repercussions such as keratitis, corneal ulcer, severe itching with skins
267 lesions, trichiasis, ectropion or entropion with corneal lesions. Combination of both systemic
268 and local treatment may also be interesting in some putative facial extensive Demodex
269 outbreaks, such as rosacea [65–67].

270

271 **Parameters influencing therapeutics**

272 In epidemiological studies, the influence of socio-demographic parameters on mites count
273 was controversial. It was described a higher prevalence of infestation in people with oily or
274 mixed skin than with dry or neutral skin [68–71], in humid-tropical climate [72], in
275 immunocompromised patients [73–77], or in childhood malnutrition [78]. Majority of studies

276 concluded on an increase of mites count with age [1,68,79,80], which may be explained by
277 the decreasing activity of the glands of Zeiss and the Meibomian glands with age [1,50,81].
278 However, in paediatric and teenage population, Demodex mites could played a pathological
279 role in recurrent chalazia, itching and redness eyelid [28,30]. Differences between socio-
280 demographic results could be explained by variability of inclusion criteria. According to
281 meta-regression results, we did not find significant influences of age and gender on mites
282 count. Most of included studies were epidemiological and recruited patients during
283 conventional examination for refractive or pre-surgical consultations. Many patients in these
284 consultations may have not complained of any symptoms whereas all patients in our study
285 were recruited because of chronic blepharitis (thus with a high probability of complaints).

286

287 **Limitations**

288 Our study had some limitations. Data collections and inclusion/exclusion criteria were not
289 identical within each studies, which may have affected our results, as well as heterogeneity
290 due to different study designs – retrospective [18,22,24,30] or prospective studies,
291 randomized [15,20,25,29,31] or not [14,16,19,21,23,26–28,32,46]. Nevertheless, we
292 combined a large number of patients and procedures to permit a large overview, with
293 sensitivity analyses (data not shown) demonstrating similar results whatever study designs.
294 Studies included small samples and were exclusively monocenter, precluding generalizability.
295 Though, all continents and all ethnicities were included. Moreover, we cover nearly 30 years
296 of treatments of Demodex blepharitis, with a wide range of therapeutics. However, the
297 apparition of new treatments precluded efficacy analyses of same treatments over time. All
298 studies used conventional parasitological examination to prove Demodex infestation. Despite
299 different number of eyelashes sampled between included studies, and thus difference between
300 studies concerning mite's count before treatment, it did not influence our results because

301 meta-analysis were on mites count changes. Other parameters evaluating efficacy of
302 treatments (e.g. tears quality [19,23], specific questionnaires [19,29,31,32,46], infrared
303 thermography [23]) were limited to few studies and differing, precluding further analyses.

304

305 **Conclusion**

306 Except usual lid hygiene for mites count, CHEO for both eradication rate and symptoms, and
307 CHEO, 2% metronidazole ointment, and systemic metronidazole for symptoms, all treatments
308 were efficient. TTO, T4O and pilocarpine gel are interesting molecules to elaborate new
309 eyewashes as first-line local treatment of Demodex blepharitis. As second-line treatment or in
310 severe cases, systemic treatment as ivermectin or metronidazole could be used in association
311 with local treatments.

312

313 **Abbreviations and Acronyms**

314 **CHEO**= Children's Hospital of Eastern Ontario (cholestyramine 5% ointment); **CONSORT**=
315 consolidated standards of reporting trials; **ES**= effect size; **INR**= International Normalized
316 Ratio; **OLSP**= Ocusoft lid scrub plus; **SIGN**= Scottish Intercollegiate Guidelines Network;
317 **STROBE**= strengthening the reporting of observational studies in epidemiology; **TTFW**= Dr
318 Organic Tea Tree Face Wash; **TTO**= tea tree oil; **T4O**= terpinen-4-ol; **US**= United State of
319 America; **95CI**= 95% confidence interval.

320

321 **Contributors**

322 CBA and FC were responsible for the design and conception of the study. VN and CBA
323 searched and collected studies and data. VN, CBA, FC and FD analysed and interpreted data.
324 AM and FD were in charge of statistical analyses. VN, CBA and FD wrote the manuscript.
325 All authors made critical revisions to the article. All authors gave their final approval of the
326 article.

327

328 **Funding**

329 None

330

331 **Competing interests**

332 The authors declare that they have no competing interests.

333

334 **Data sharing statement**

335 No additional data are available

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568

569 **Figures legends**

570

571 **Figure 1.** Search strategy

572 **Figure 2.** Methodological quality of included cohort articles using the SIGN model.

573 **Figure 3.** Summary bias risk of included cohort studies and controlled trials articles using the
574 SIGN model.

575 **Figure 4.** Meta-analysis on mite's count, eradication rate and symptoms improvement rate in
576 each treatment protocol (95% CI: 95% Confidence intervals)

577 **Figure 5.** Meta-analysis on mite's count, eradication rate and symptoms improvement rate in
578 each treatment protocol (95% CI: 95% Confidence intervals)

579 **Figure 6.** Meta-regressions about parameters of analyses (95% CI: 95% Confidence intervals)

580 **Figure 7.** Meta-analysis on mite's count, eradication rate and symptoms improvement rate in
581 each treatment type (95% CI: 95% confidence intervals)

582 **Appendix 1.** Details on study characteristics, quality of articles (Figures 2 and 3), method of
583 Demodex identification, type of treatments, protocol for each treatment, inclusion and
584 exclusion criteria of each included study, population, aims and outcomes of included studies

585 **Appendix 2.** Meta-analysis on mite's count in each treatment protocol (95% CI: 95%
586 confidence intervals)

587 **Appendix 3.** Meta-analysis on eradication rate in each treatment protocol (95% CI: 95%
588 confidence intervals)

589 **Appendix 4.** Meta-analysis on symptoms improvement rate in each treatment protocol (95%
590 CI: 95% confidence intervals)

591 **Appendix 5.** Meta-analysis on mite's count, eradication rate and symptoms improvement rate
592 in each eyelash sampling method (95% CI: 95% confidence intervals)

Identification

Keywords used for search strategy:
(blepharitis OR blepharitides) AND (drug* OR pharmacotherapy OR therap* OR treat* OR administration OR patient* OR outcome* OR efficacy OR effective* OR clinical OR management OR compliance OR adherence)

Screening

Pubmed
n=1236

Cochrane
n=820

Embase
n=725

ClinicalTrial.gov
n=15

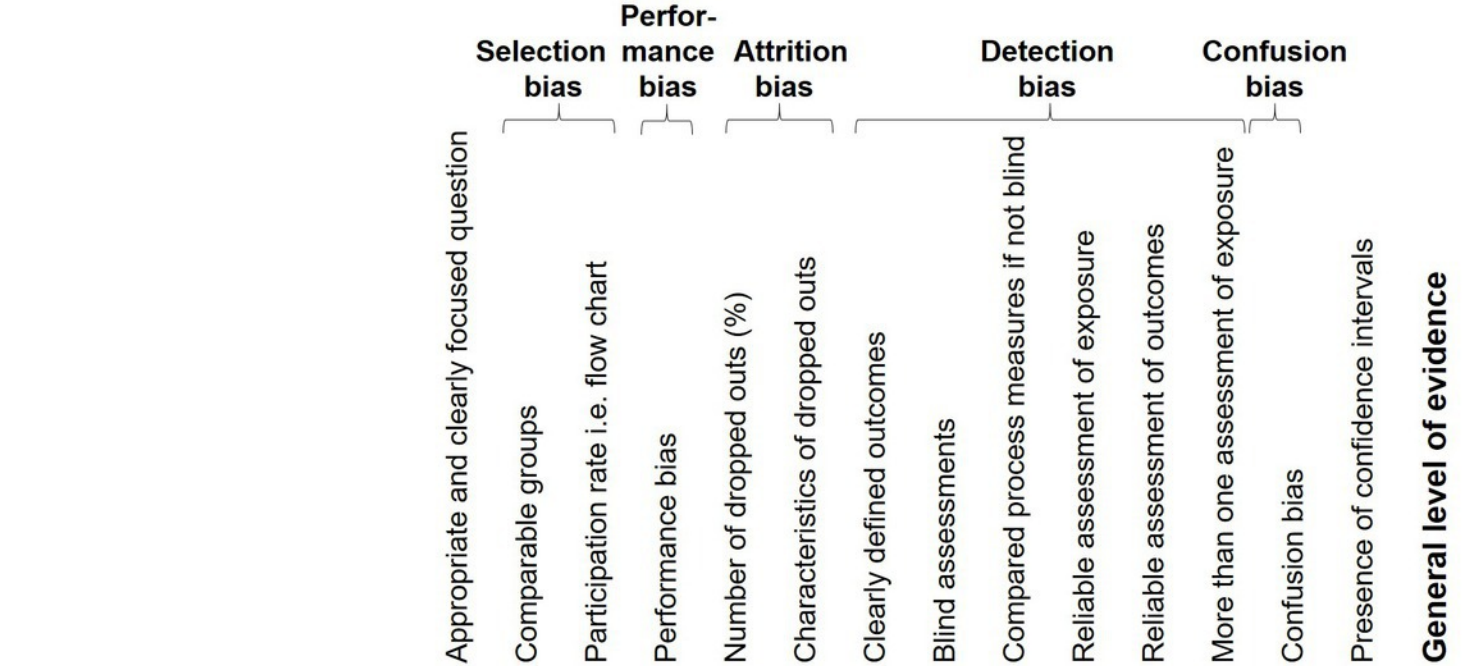
Eligibility

Potential eligible articles
N= 2796

- Duplicates removed n=913
- Studies not in French, English or Spanish n=52
- Off topic studies n=1741
- Data not available n=71

Included

Included studies
n=19



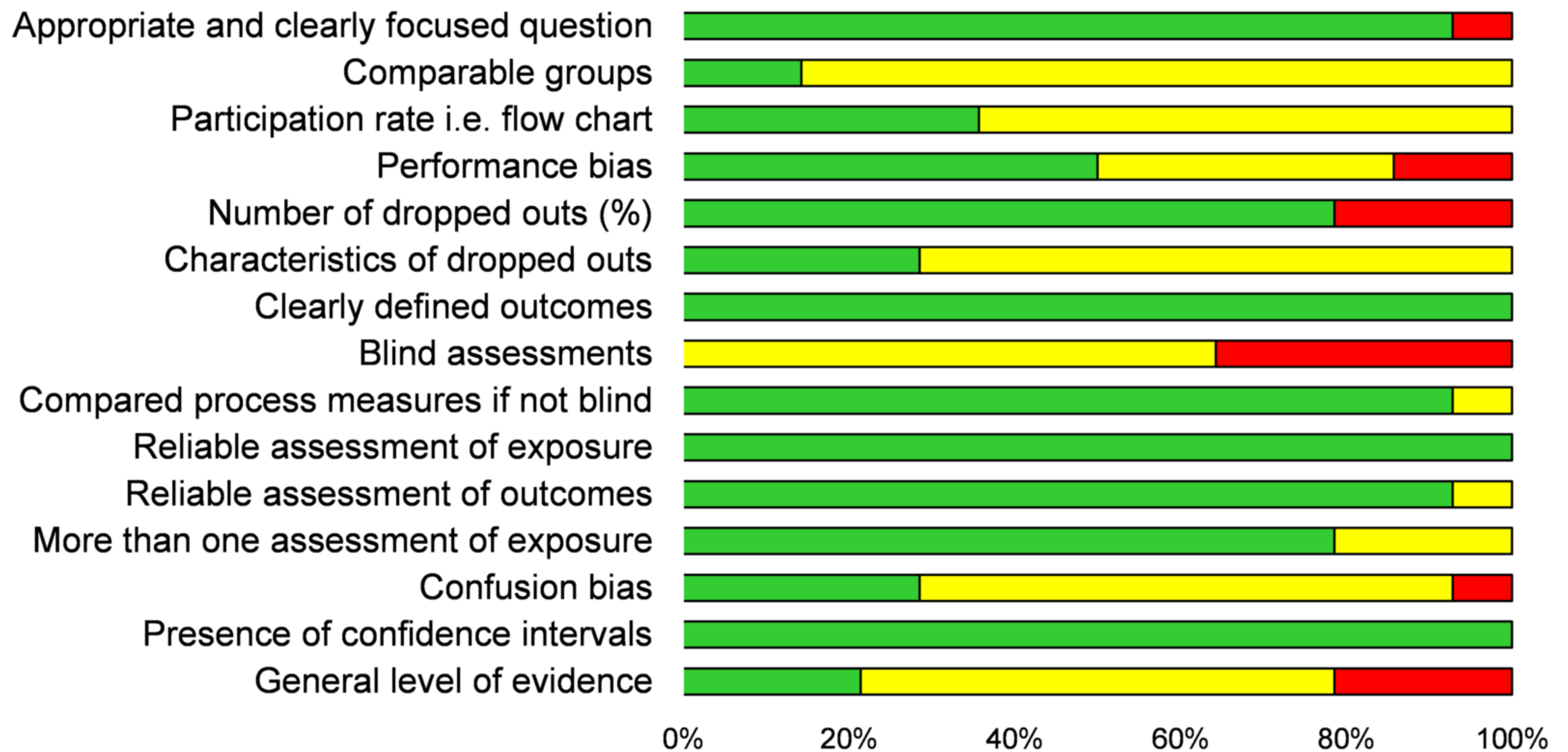
| | Selection bias | | Performance bias | Attrition bias | | Detection bias | | | | Confusion bias | | | General level of evidence | | | |
|----------------------|--|-------------------|------------------------------------|------------------|----------------------------|---------------------------------|--------------------------|-------------------|--|---------------------------------|---------------------------------|--------------------------------------|---------------------------|----------------|----------------------------------|---|
| | Appropriate and clearly focused question | Comparable groups | Participation rate i.e. flow chart | Performance bias | Number of dropped outs (%) | Characteristics of dropped outs | Clearly defined outcomes | Blind assessments | Compared process measures if not blind | Reliable assessment of exposure | Reliable assessment of outcomes | More than one assessment of exposure | | Confusion bias | Presence of confidence intervals | |
| Alver 2017 | + | NA | NA | - | 7 | NA | + | NA | + | + | + | + | + | + | + | |
| Filho 2011 | + | NA | NA | + | 30 | NA | + | NA | ? | + | + | + | + | ? | + | 0 |
| Fulk 1996 | + | + | + | + | 9 | + | + | - | + | + | + | + | + | + | + | + |
| Gao 2005 | + | ? | + | ? | 0 | + | + | - | + | + | + | + | + | ? | + | + |
| Gao 2007 | + | NA | NA | + | 0 | NA | + | NA | + | + | + | + | + | ? | + | + |
| Gao 2012 | + | ? | + | ? | 0 | + | + | - | + | + | + | + | + | ? | + | + |
| Hirsch-Hoffmann 2015 | + | ? | + | ? | 8 | NA | + | - | + | + | + | NA | + | + | + | + |
| Holzchuh 2010 | + | NA | NA | + | 0 | NA | + | NA | + | + | + | + | + | ? | + | + |
| Kheirkhah 2007 | + | NA | NA | ? | 0 | NA | + | NA | + | + | + | NA | ? | + | + | + |
| Kim 2011 | + | NA | NA | + | 0 | NA | + | NA | + | + | + | + | + | ? | + | + |
| Liang 2010 | + | + | + | + | 0 | + | + | - | + | + | ? | NA | ? | + | + | + |
| Liang 2017 | + | NA | NA | + | 4 | NA | + | NA | + | + | + | + | + | + | + | + |
| Nicholls 2016 | + | NA | NA | ? | 30 | NA | + | NA | + | + | + | + | + | ? | + | 0 |
| Rodriguez 2005 | - | NA | NA | - | 30 | NA | + | NA | + | + | + | + | + | - | + | 0 |

| | | | | | | | | | | | |
|--------------|---|---|---|---|---|---|---|----|---|----|---|
| Koo 2012 | + | + | ? | + | + | + | + | 0 | + | NA | + |
| Murphy 2017 | + | + | ? | + | + | + | + | 43 | + | NA | 0 |
| Salem 2012 | + | ? | ? | + | + | + | + | 0 | + | NA | + |
| Tseng 2018 | + | + | + | + | + | + | + | 0 | + | NA | + |
| Celorio 1989 | + | + | + | + | + | + | + | 12 | + | NA | + |

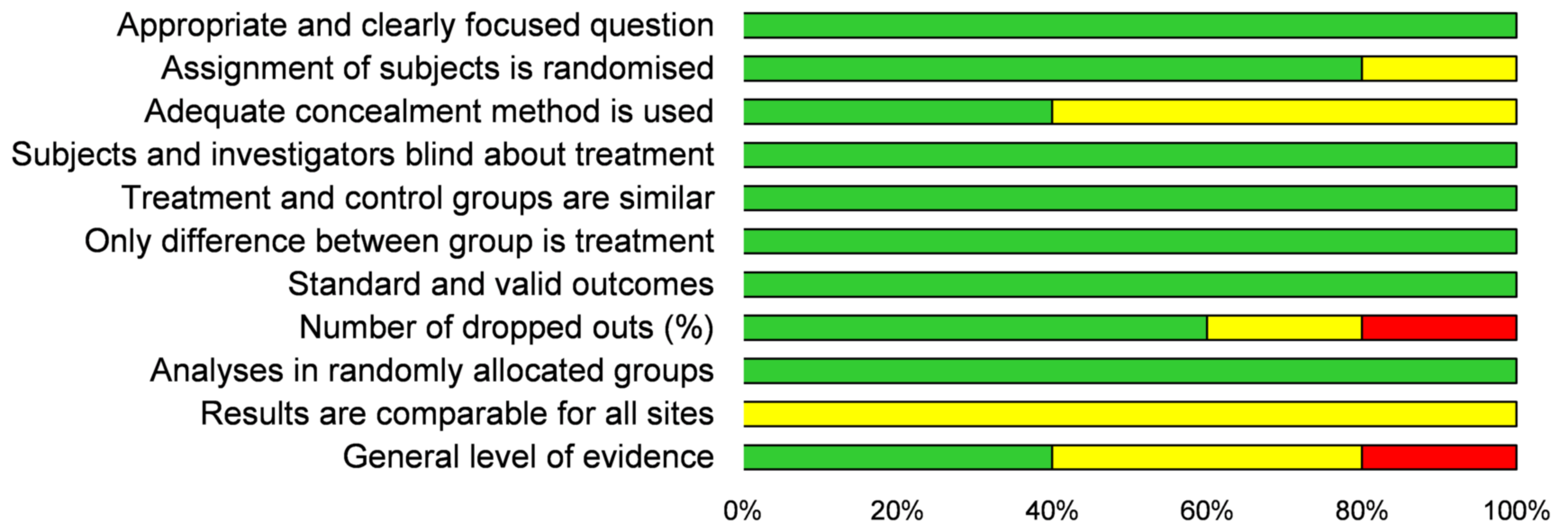
| | Appropriate and clearly focused question | Assignment of subjects is randomised | Adequate concealment method is used | Subjects and investigators blind about treatment | Treatment and control groups are similar | Only difference between group is treatment | Standard and valid outcomes | Number of dropped outs (%) | Analyses in randomly allocated groups | Results are comparable for all sites | General level of evidence |
|--------------|--|--------------------------------------|-------------------------------------|--|--|--|-----------------------------|----------------------------|---------------------------------------|--------------------------------------|---------------------------|
| Koo 2012 | + | + | ? | + | + | + | + | 0 | + | NA | + |
| Murphy 2017 | + | + | ? | + | + | + | + | 43 | + | NA | 0 |
| Salem 2012 | + | ? | ? | + | + | + | + | 0 | + | NA | + |
| Tseng 2018 | + | + | + | + | + | + | + | 0 | + | NA | + |
| Celorio 1989 | + | + | + | + | + | + | + | 12 | + | NA | + |

Risk of bias summary

Cohort Studies



Controlled Trials



■ low risk of bias ■ unclear risk of bias ■ high risk of bias

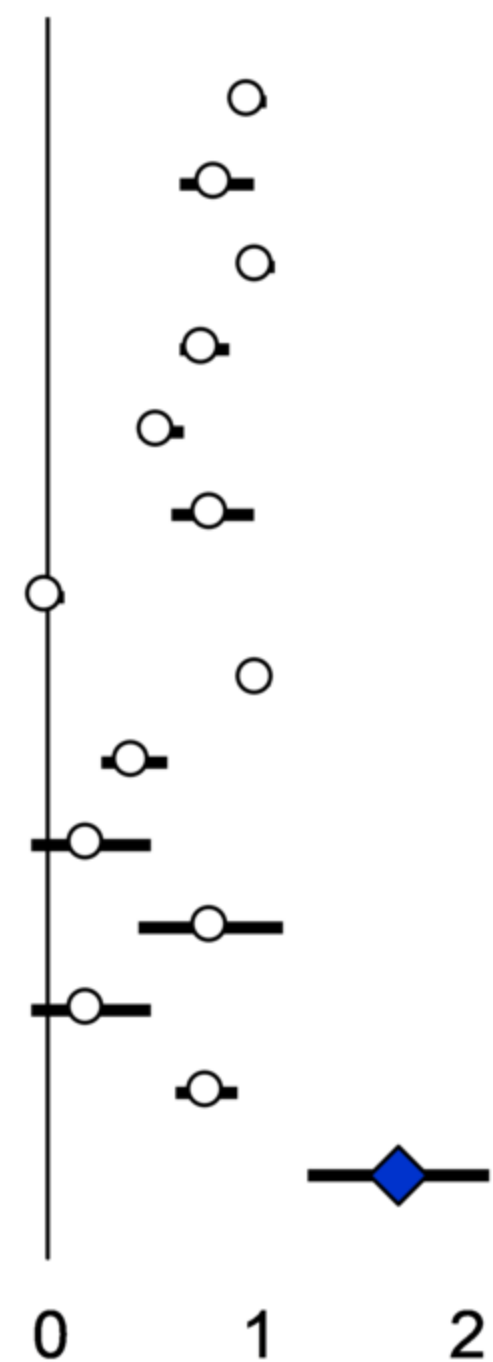
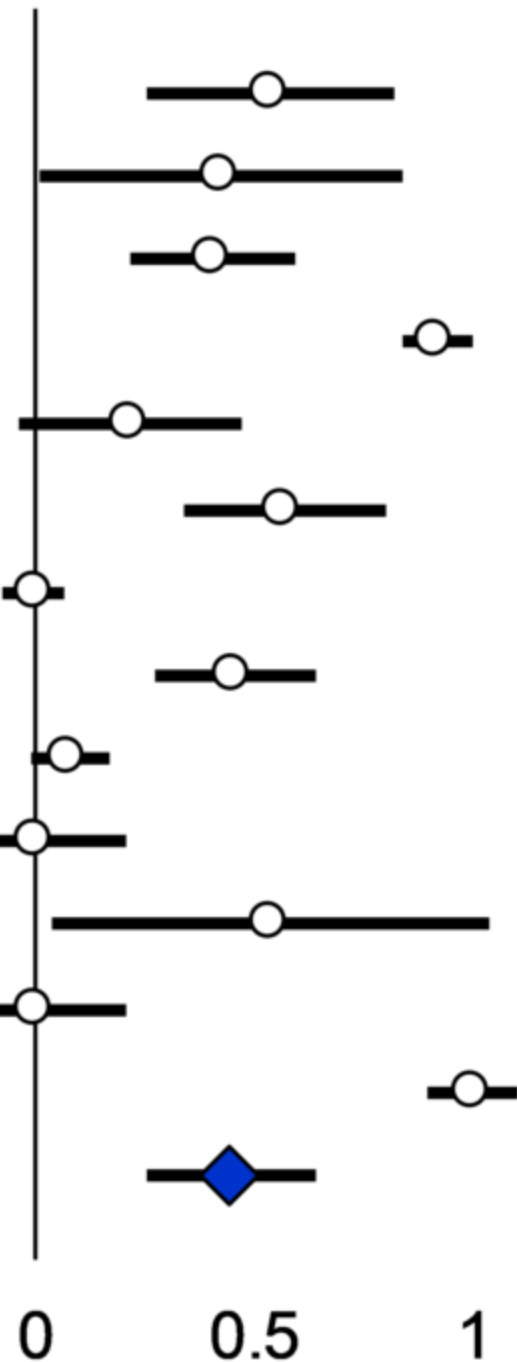
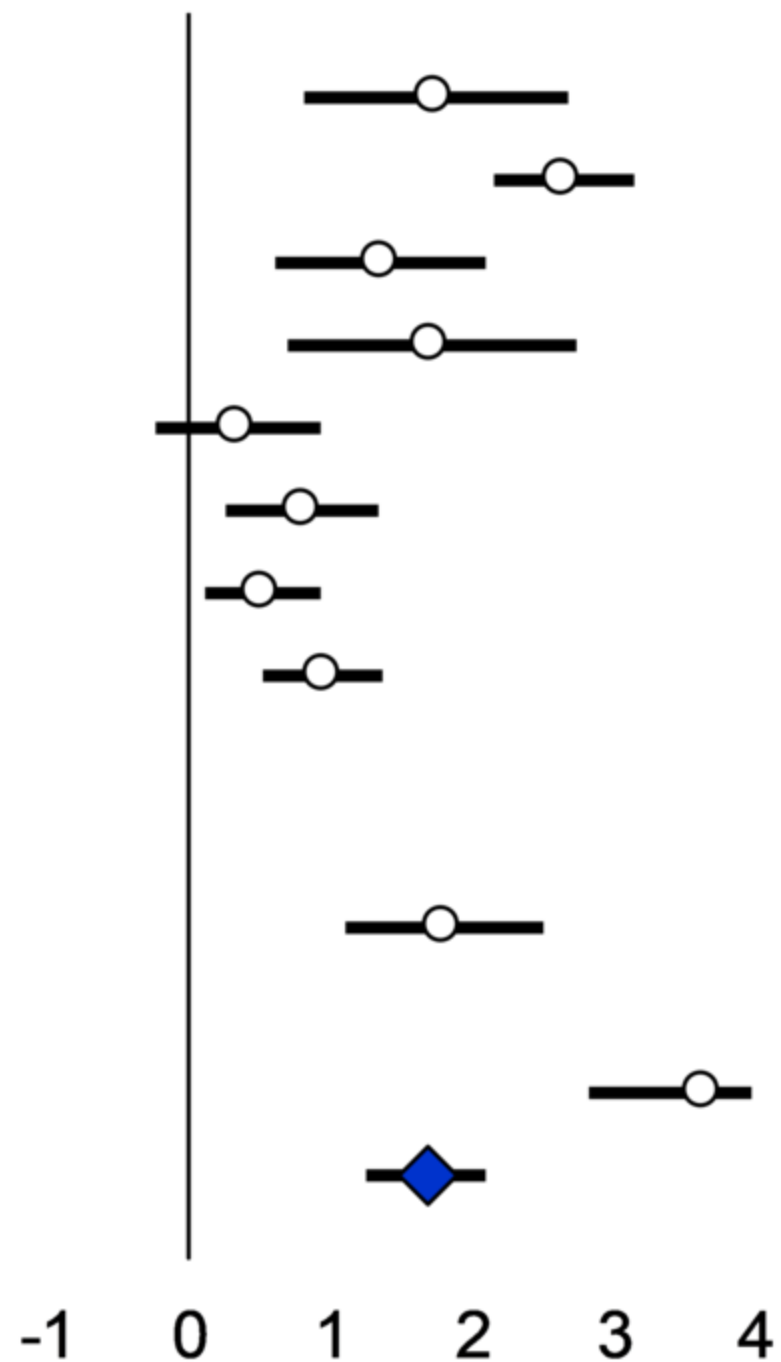
Treatment

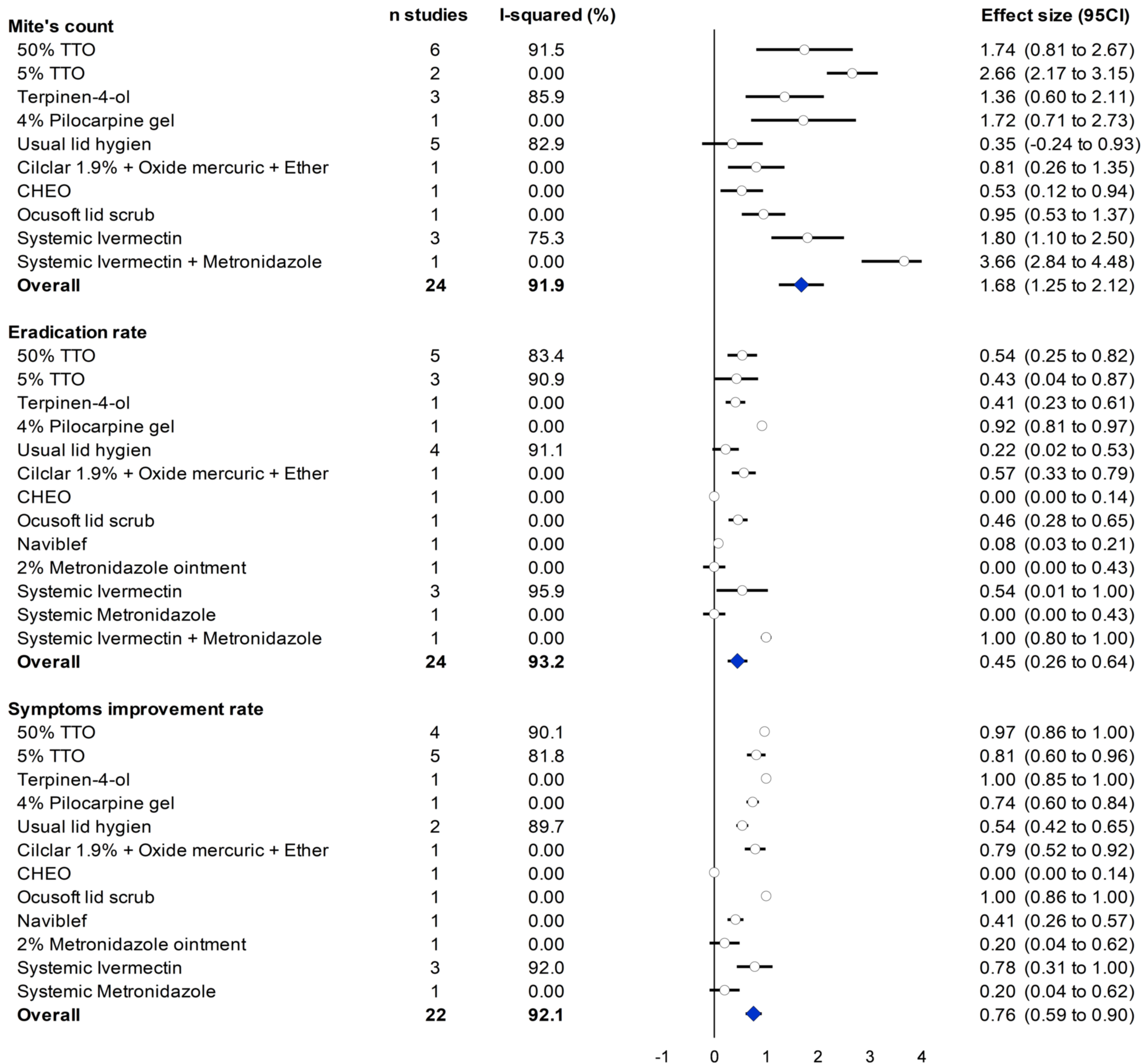
Mite's count

Eradication rate

Symptoms improvement rate

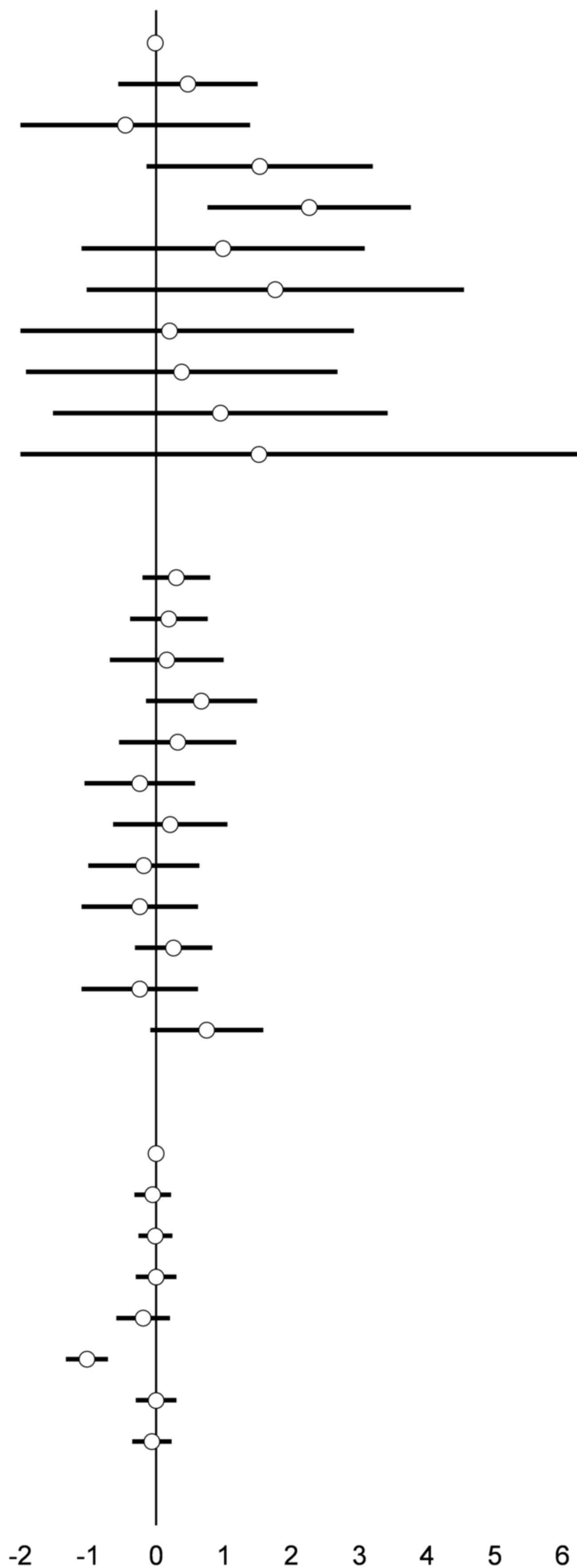
- 50% TTO
- 5% TTO
- Terpinen-4-ol
- 4% Pilocarpine gel
- Usual lid hygien
- Cilclar 1.9% + Oxide mercuric + Ether
- CHEO
- Ocusoft lid scrub
- Naviblef
- 2% Metronidazole ointment
- Systemic Ivermectin
- Systemic Metronidazole
- Systemic Ivermectin + Metronidazole
- Overall**





Mite's count

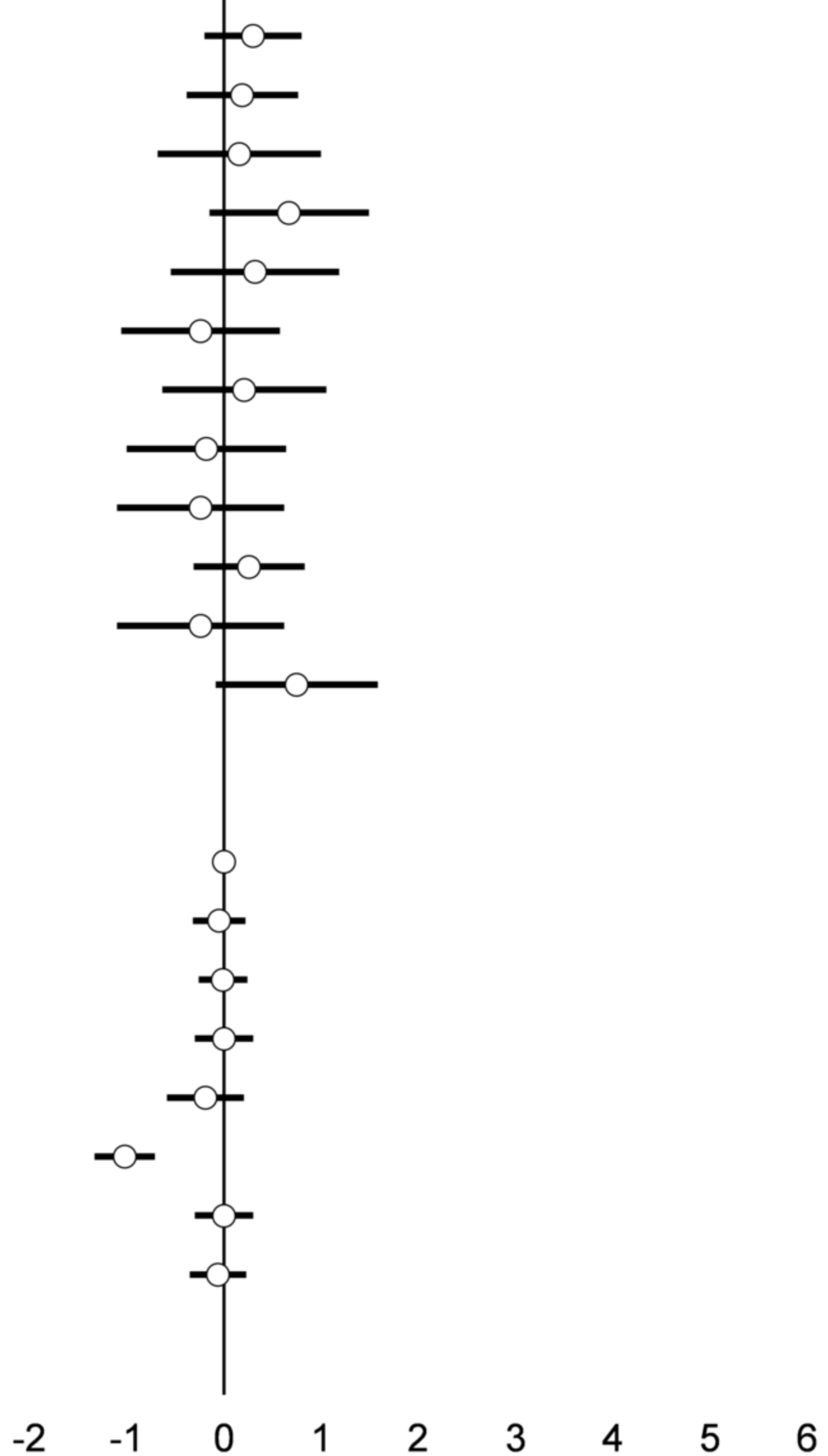
Age, years
Sex ratio (Men/Women)
Eyelash sampling method
50% TTO
5% TTO
Terpinen-4-ol
4% Pilocarpine gel
Cilclar 1,9%
CHEO
Systemic Ivermectin
Systemic Ivermectin + Metronidazole



| | coefficient (95CI) | p-value |
|-------------------------------------|-----------------------|---------|
| Age, years | -0.01 (-0.05 to 0.02) | 0.49 |
| Sex ratio (Men/Women) | 0.47 (-0.56 to 1.50) | 0.31 |
| Eyelash sampling method | -0.45 (-2.30 to 1.38) | 0.58 |
| 50% TTO | 1.53 (-0.14 to 3.20) | 0.07 |
| 5% TTO | 2.26 (-0.50 to 2.50) | 0.05 |
| Terpinen-4-ol | 0.99 (-1.10 to 3.08) | 0.30 |
| 4% Pilocarpine gel | 1.76 (-1.03 to 4.54) | 0.18 |
| Cilclar 1,9% | 0.20 (-2.52 to 3.92) | 0.87 |
| CHEO | 0.38 (-1.90 to 2.70) | 0.71 |
| Systemic Ivermectin | 0.95 (-1.50 to 3.44) | 0.40 |
| Systemic Ivermectin + Metronidazole | 1.52 (-3.30 to 6.39) | 0.48 |

Eradication rate

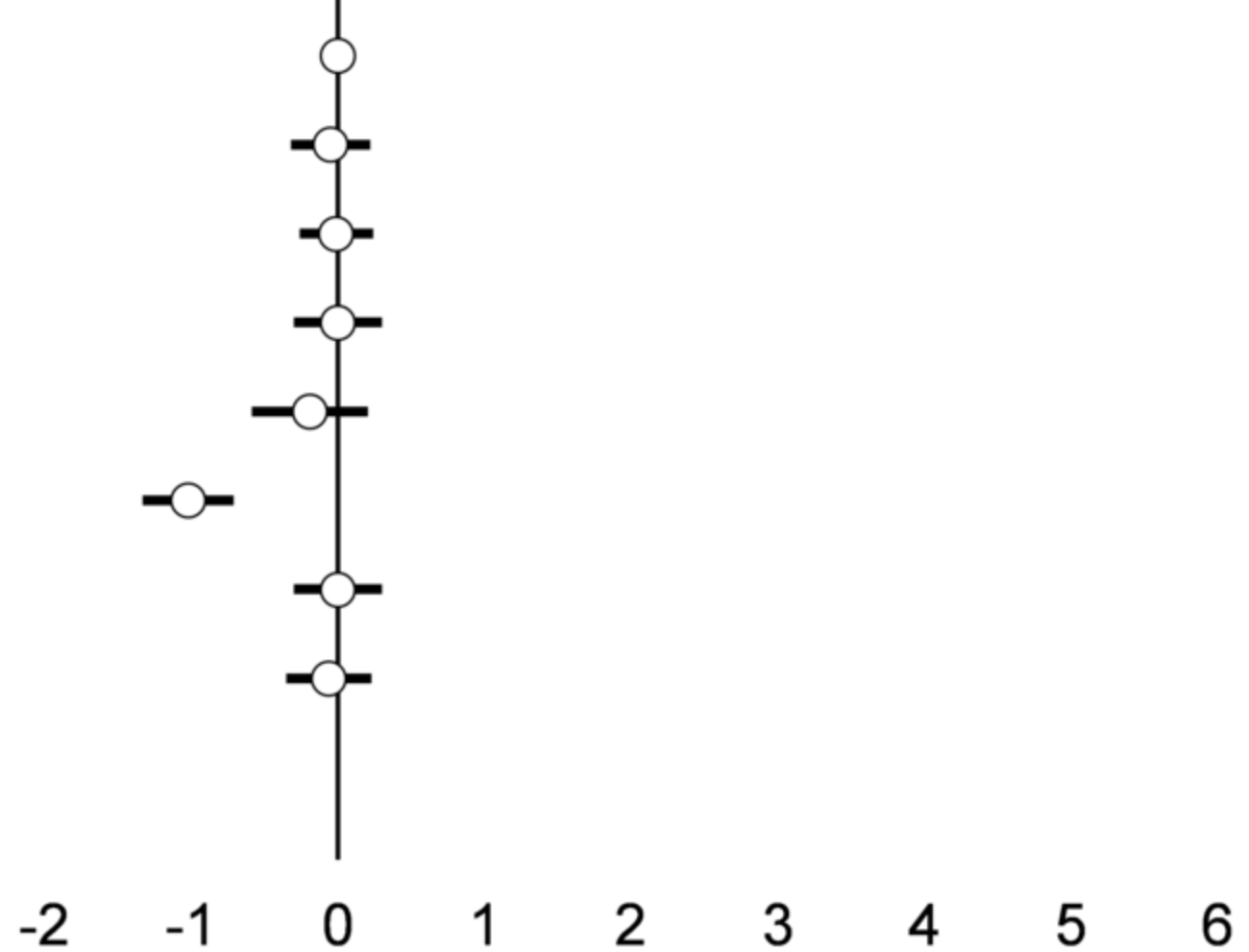
50% TTO
5% TTO
Terpinen-4-ol
4% Pilocarpine gel
Cilclar 1,9%
CHEO
Ocusoft lid scrub
Naviblef
2% Metronidazole ointment
Systemic Ivermectin
Systemic Metronidazole
Systemic Ivermectin + Metronidazole



| | | |
|-------------------------------------|-----------------------|------|
| 50% TTO | 0.30 (-0.20 to 0.80) | 0.21 |
| 5% TTO | 0.19 (-0.38 to 0.77) | 0.47 |
| Terpinen-4-ol | 0.16 (-0.68 to 1.00) | 0.68 |
| 4% Pilocarpine gel | 0.67 (-0.14 to 1.50) | 0.09 |
| Cilclar 1,9% | 0.32 (-0.54 to 1.19) | 0.43 |
| CHEO | -0.24 (-1.06 to 0.57) | 0.52 |
| Ocusoft lid scrub | 0.21 (-0.63 to 1.06) | 0.59 |
| Naviblef | -0.18 (-1.00 to 0.64) | 0.63 |
| 2% Metronidazole ointment | -0.24 (-1.10 to 0.62) | 0.55 |
| Systemic Ivermectin | 0.26 (-0.30 to 0.84) | 0.33 |
| Systemic Metronidazole | -0.24 (-1.10 to 0.62) | 0.55 |
| Systemic Ivermectin + Metronidazole | 0.75 (-0.07 to 1.60) | 0.07 |

Symptoms improvement rate

Age, years
50% TTO
5% TTO
Terpinen-4-ol
Cilclar 1,9%
CHEO
Ocusoft lid scrub
Systemic Ivermectin



| | | |
|---------------------|------------------------|------------------|
| Age, years | 0.00 (-0.01 to 0.04) | 0.51 |
| 50% TTO | -0.05 (-0.32 to 0.22) | 0.68 |
| 5% TTO | -0.01 (-0.39 to 0.11) | 0.21 |
| Terpinen-4-ol | 0.00 (-0.30 to 0.30) | 0.99 |
| Cilclar 1,9% | -0.19 (-0.59 to 0.20) | 0.27 |
| CHEO | -1.02 (-1.33 to -0.71) | <0.001 |
| Ocusoft lid scrub | 0.00 (-0.30 to 0.30) | 0.99 |
| Systemic Ivermectin | -0.06 (-0.35 to 0.23) | 0.62 |

