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# Efficacy of treatments for Demodex blepharitis:

## a systematic review and meta-analysis

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## Abstract

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

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

**Results:** We included 19 studies (14 observational and 5 randomized clinical trials), for a total of 934 patients, 1741 eyes, and 13 different treatments. For mites count, eradication rate, and symptoms improvement, meta-analysis included fifteen, fourteen and thirteen studies, respectively. The overall effect sizes for efficiency of all treatments, globally, were 1.68 (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 hygiene for mites count, Children's Hospital of Eastern Ontario ointment (CHEO) for both eradication rate and symptoms, and CHEO, 2% metronidazole ointment, and systemic metronidazole for symptoms, all treatments were efficient. Stratified meta-analysis did not show significant differences between local and systemic treatments (1.22, 0.83 to 1.60 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 rate; and 0.77, 0.58 to 0.92 vs 0.67, 0.25 to 0.98 for symptoms improvement).

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

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

## Introduction

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

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

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

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

## **Methods**

### **Literature search**

We have searched all articles in PubMed, The Cochrane Library, Central, Embase, ClinicalTrial.gov, Google Scholar and ScienceDirect databases from February 2018 to August 2018 with following keywords: (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). We limited our search to articles written in English, French, or Spanish. No minimal sample size was applied. To be included, articles needed to evaluate a therapy concerning Demodex blepharitis proved by parasitological examination or confocal microscopy or cylindrical dandruff. We imposed no limitation of regional origin or control group nature. In addition, references list of all publications was manually searched to identify any other ones not found with electronic search. The search strategy is presented in Figure 1. One author conducted all literature searches (Valentin Navel) and collated the abstracts. Two authors (Valentin Navel and Cédric Benoist d'Azy) separately reviewed the abstracts and based on the selection criteria, decided the suitability of the articles for inclusion. A third author (Frédéric Dutheil) was asked to review the articles where consensus on suitability was debated. Finally, all authors reviewed eligible articles.

## **Quality of assessment**

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

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

## **Statistical considerations**

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

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

## Results

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

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

### Meta-analyses and meta-regressions

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

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

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

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



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

## **Discussion**

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

## **Rational of study**

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

physiological a number of mites <5 mites/cm<sup>2</sup> for skin lesions or <3 mites at the root of each eyelash [4,20,47]. However, mites outbreaks may play a role in the pathophysiology of the infection, causing a local inflammatory reaction and a repercussion on the ocular surface [1,5,8,9,13,48–50]. Therefore, several therapeutics were used such as antiparasitic, antiseptics, or anti-inflammatory drugs. Our meta-analysis was needed because most treatments were used without sound proof of efficiency and without randomized controlled trials comparing efficiency of treatments. We chose Demodex count as primary judgement criteria because the presence of some mites may be considered as normal and outbreaks pathological. Eradication rate was chosen as a secondary judgement criteria to evaluate the in vivo killing effect in parallel of mites count decrease.

## **Interest molecules**

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

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

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

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

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

### **Parameters influencing therapeutics**

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

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

## **Limitations**

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

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

## **Conclusion**

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

## **Abbreviations and Acronyms**

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

## **Contributors**

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

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## **Competing interests**

The authors declare that they have no competing interests.

## **Data sharing statement**

No additional data are available

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## Figures legends

**Figure 1.** Search strategy

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

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

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

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

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

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

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

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

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

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

**Appendix 5.** Meta-analysis on mite's count, eradication rate and symptoms improvement rate 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



Cohort studies

Alver 2017	<div>+</div>	<div>NA</div>	<div>NA</div>	<div>-</div>	<div>7</div>	<div>NA</div>	<div>+</div>	<div>NA</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	
Filho 2011	<div>+</div>	<div>NA</div>	<div>NA</div>	<div>+</div>	<div>30</div>	<div>NA</div>	<div>+</div>	<div>NA</div>	<div>?</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>?</div>	<div>+</div>	<div>0</div>
Fulk 1996	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>9</div>	<div>+</div>	<div>+</div>	<div>-</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>
Gao 2005	<div>+</div>	<div>?</div>	<div>+</div>	<div>?</div>	<div>0</div>	<div>+</div>	<div>+</div>	<div>-</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>?</div>	<div>+</div>	<div>+</div>
Gao 2007	<div>+</div>	<div>NA</div>	<div>NA</div>	<div>+</div>	<div>0</div>	<div>NA</div>	<div>+</div>	<div>NA</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>?</div>	<div>+</div>	<div>+</div>
Gao 2012	<div>+</div>	<div>?</div>	<div>+</div>	<div>?</div>	<div>0</div>	<div>+</div>	<div>+</div>	<div>-</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>?</div>	<div>+</div>	<div>+</div>
Hirsch-Hoffmann 2015	<div>+</div>	<div>?</div>	<div>+</div>	<div>?</div>	<div>8</div>	<div>NA</div>	<div>+</div>	<div>-</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>NA</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>
Holzchuh 2010	<div>+</div>	<div>NA</div>	<div>NA</div>	<div>+</div>	<div>0</div>	<div>NA</div>	<div>+</div>	<div>NA</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>?</div>	<div>+</div>	<div>+</div>
Kheirkhah 2007	<div>+</div>	<div>NA</div>	<div>NA</div>	<div>?</div>	<div>0</div>	<div>NA</div>	<div>+</div>	<div>NA</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>NA</div>	<div>?</div>	<div>+</div>	<div>+</div>	<div>+</div>
Kim 2011	<div>+</div>	<div>NA</div>	<div>NA</div>	<div>+</div>	<div>0</div>	<div>NA</div>	<div>+</div>	<div>NA</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>?</div>	<div>+</div>	<div>+</div>
Liang 2010	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>0</div>	<div>+</div>	<div>+</div>	<div>-</div>	<div>+</div>	<div>+</div>	<div>?</div>	<div>NA</div>	<div>?</div>	<div>+</div>	<div>+</div>	<div>+</div>
Liang 2017	<div>+</div>	<div>NA</div>	<div>NA</div>	<div>+</div>	<div>4</div>	<div>NA</div>	<div>+</div>	<div>NA</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>
Nicholls 2016	<div>+</div>	<div>NA</div>	<div>NA</div>	<div>?</div>	<div>30</div>	<div>NA</div>	<div>+</div>	<div>NA</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>?</div>	<div>+</div>	<div>0</div>
Rodriguez 2005	<div>-</div>	<div>NA</div>	<div>NA</div>	<div>-</div>	<div>30</div>	<div>NA</div>	<div>+</div>	<div>NA</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>+</div>	<div>-</div>	<div>+</div>	<div>0</div>

Controlled Trials studies

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

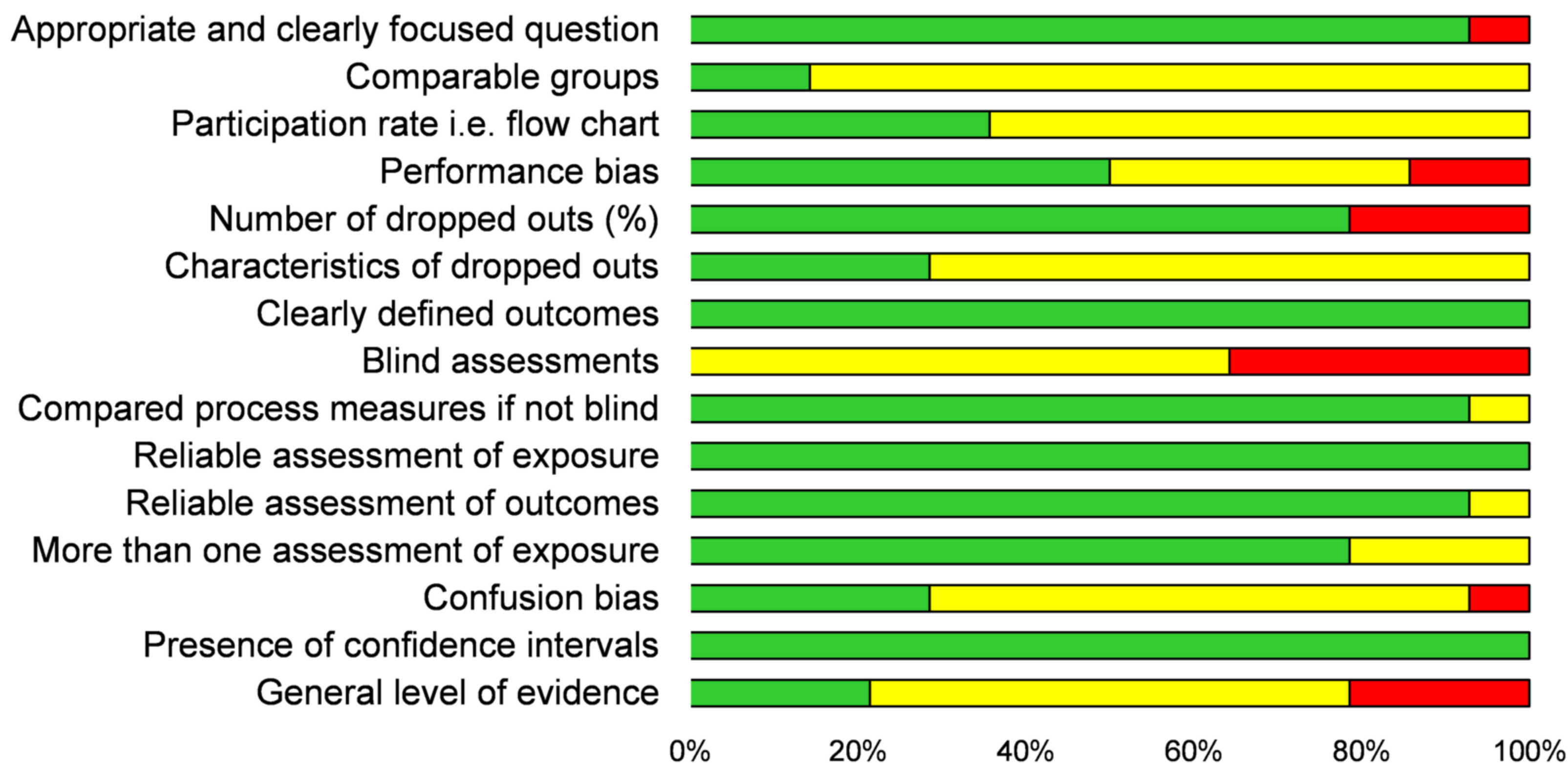
Results are comparable for all sites

General level of evidence

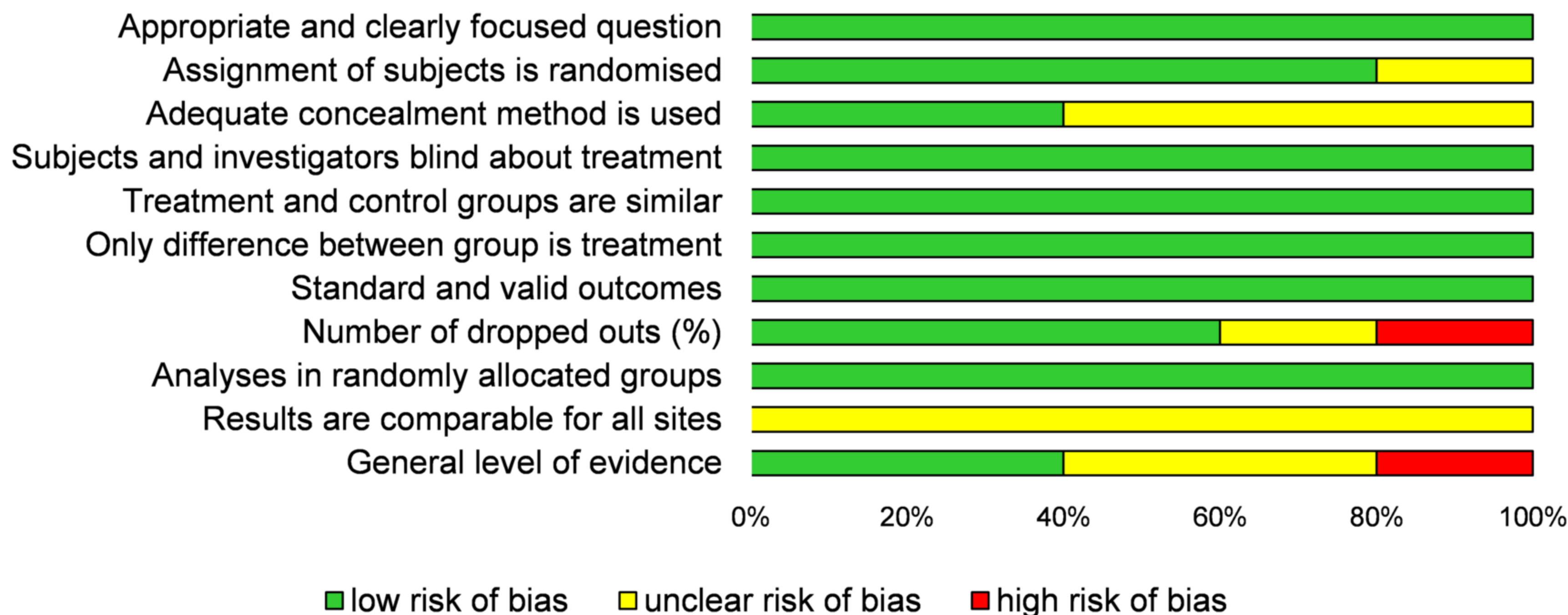


# Risk of bias summary

## Cohort Studies



## Controlled Trials



# Treatment

## Mite's count

## Eradication rate

## Symptoms improvement rate

