National Institute for Health and Care Excellence

Insect bites and stings: antimicrobial prescribing

Evidence review

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Draft for consultation

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1 Context

1.1 Background

An insect bite or sting often causes a small, red lump on the skin, which may be painful and itchy. Most insect bites will heal within a few hours or days, although some larger local reaction can take around 10 days to resolve (NICE CKS – insect bites and stings 2016), and can be treated at home following simple advice (NHS 2016). However, complications from insect bites and stings include allergic reactions, systemic toxicity (from multiple stings), transmission of infectious diseases (such as Lyme disease or malaria) local skin trauma, and secondary skin infections (NICE CKS – Insect bites and stings 2016).

In the UK, insect stings are the second commonest cause of anaphylaxis outside the medical setting (NICE CKS – Insect bites and stings 2016). Anaphylaxis and other systemic reactions or toxicity caused by insect bites or stings are outside the scope of this guideline, please see the NICE guideline on Anaphylaxis (2011). Similarly, infections transmitted by insect bites (such as Lyme disease and malaria) are out of scope for this guideline, for information on the diagnosis and management of Lyme disease please see the NICE guideline on Lyme disease (2018).

This guideline will focus on the management of small (redness, swelling, itching and pain) and large (larger areas of redness, swelling, itching) local skin reactions or trauma and secondary skin infections. However, prevention is also important, in a recent survey of GPs (Anderson et al 2019) over half of respondents (61%) stated that they advocated prevention of insect bites and stings to their patients using an insect repellent, with 31% advising about prevention using clothing and nets.

It has been suggested that insect bites and stings are common in the UK but exact data on incidence is unknown as most bites and stings are not reported (DTB 2012). It has been estimated that the weekly average (mean) incidence of all age insect bites is 5.4 per 100,000, for all-ages and genders of people presenting to a GP in England and Wales (Elliot et al 2006). A recent survey of 199 GPs (Anderson et al 2019) found that all respondent GPs had managed an insect bite in the previous 12 months, with estimated numbers ranging from less than 5 to 100 bites, and 71% reported seeing an infected bite in the previous 12 months. However, incidence varies by season being more common in the summer months when insects are more active and skin more exposed (NICE CKS – Insect bites and stings 2016).

It is not uncommon for people to be unable to identify what they are bitten or stung by as they may not see it happen, however the treatment is similar for most bites and stings (NHS 2016).

A systematic review (Anderson et al 2019) found no data from the UK on the number of cases of infection secondary to insect bites or stings but it is thought that both cellulitis (NICE CKS – insect bites and stings) and impetigo (Elliot et al 2006) may be associated.

Most insect bites and stings cause no infection and are self-limiting in nature. Treatment, where required, will generally be first aid treatment (for example removal of stings or ticks, or rest, ice compression and elevation) or medicines for symptom relief (for example antihistamines for swelling and pruritus, or oral analgesia for pain). In infected insect bites and stings, the most common causative pathogens are largely unknown.

A recent survey of 199 GPs (Anderson et al 2019) in the UK found that 80% of respondents had prescribed flucloxacillin for an infected bite, but other antibiotics had also been prescribed (co-amoxiclav, phenoxymethylpenicillin, amoxicillin and topical fusidic acid), with rates of investigation, referral and hospital admission found to be low.

1.2 Antimicrobial stewardship

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) provides recommendations for prescribers for prescribing antimicrobials. The recommendations guide prescribers in decisions about antimicrobial prescribing and include recommending that prescribers follow local and national guidelines, use the shortest effective course length and record their decisions, particularly when these decisions are not in line with guidelines. The recommendations also advise that prescribers take into account the benefits and harms for a person when prescribing an antimicrobial, such as possible interactions, co-morbidities, drug allergies and the risks of healthcare associated infections.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that resources and advice should be available for people who are prescribed antimicrobials to ensure they are taken as instructed at the correct dose, via the correct route, for the time specified. Verbal advice and written information that people can take away about how to use antimicrobials correctly should be given, including not sharing prescription-only antimicrobials with anyone other than the person they were prescribed or supplied for, not keeping them for use another time and returning unused antimicrobials to the pharmacy for safe disposal and not flushing them down toilets or sinks.

In line with the Public Health England guidance (Start Smart Then Focus) and the NICE guideline on antimicrobial stewardship, intravenous antibiotic prescriptions should be reviewed at 48 to 72 hours, documenting response to treatment and any available microbiology results to determine if the antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic.

1.3 Antimicrobial resistance

The consumption of antimicrobials is a major driver for the development of antibiotic resistance in bacteria, and the 3 major goals of antimicrobial stewardship are to:

- optimise therapy for individual patients
- prevent overuse, misuse and abuse, and
- minimise development of resistance at patient and community levels.

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) recommends that the risk of antimicrobial resistance for individual patients and the population as a whole should be taken into account when deciding whether or not to prescribe an antimicrobial.

When antimicrobials are necessary to treat an infection that is not life-threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these ‘last-line’ broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as *C. difficile*. For infections that are not life-threatening, broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) need to be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective (CMO report 2011).

2 Evidence selection

A range of evidence sources are used to develop antimicrobial prescribing guidelines. These fall into 2 broad categories:

- Evidence identified from the literature search (see section 2.1 below)
- Evidence identified from other information sources. Examples of other information sources used are shown in the interim process guide (2017).

See appendix A: evidence sources for full details of evidence sources used for acute sinusitis.

2.1 Literature search

A literature search was developed to identify evidence for the effectiveness and safety of interventions for managing insect bites and stings (see appendix C: literature search strategy for full details). The literature search identified 1,873 references. These references were screened using their titles and abstracts and 26 full text references were obtained and assessed for relevance. Five full text references were assessed as relevant to the guideline, this included 1 systematic review and 2 randomised controlled trials (RCTs) which were in people with mosquito bites. Due to a lack of RCT or systematic review data in any other insect bite or sting, observational studies were assessed for inclusion and 1 retrospective case series were assessed as relevant to the guideline review question (see appendix B: review protocol). One additional relevant RCT (with a subgroup of people with arthropod bites) was identified by the committee and included in this review. 10% percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%.

The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. All 5 references were included in this evidence review (see appendix : included studies).

The remaining 22 references were excluded. These are listed in appendix H: excluded studies with reasons for their exclusion.

See also appendix D: study flow diagram.

2.2 Summary of included studies

A summary of the included studies is shown in Tables 1 Table 1and 2. Details of the study citation can be found in appendix E: included studies. An overview of the quality assessment of each included study is shown in appendix F: quality assessment of included studies.

No studies on antibiotic dose, dose frequency, antibiotic course length or route of administration were identified. Only 1 RCT looked at antibiotic choice in insect bites or stings but this was a subgroup of a larger study of skin and soft tissue infection. There was a paucity of evidence for antimicrobials, and other treatments, in the care of secondary infected insect bites and stings.

Table 1: Summary of included studies: non-antimicrobial interventions

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Dyachenko and Rozenman 2006 Retrospective Case series Israel	n=52	Hospitalised adults and children (aged 9 to 66 years) with an uninfected bite (definite or presumed to be caused by a brown recluse spider)	Included[1] prophylactic antibiotics, rest, cold compress and elevation, corticosteroids, antihistamines and NSAIDs	No comparison	Time to healing and length of hospital stay
Foex et al 2006 Systematic review of Double blind, crossover[2] RCT European	7 RCTs N=180	Adults and children (bite sensitive individuals in 4 RCTs) exposed to mosquito bites	Oral antihistamines (cetirizine, ebastine and loratadine)	Placebo in 6 RCTs and one 4 arm comparison trial (cetirizine, ebastine, loratadine and placebo)	Skin reaction and pruritus
Karpinnen et al 2006 Double blind, crossover RCT Finland	N=29	Bite sensitive adults (aged 19 to 64 years) exposed to bites from mosquitos	Oral antihistamine (levocetirizine)	Placebo	Skin reaction and pruritus
Karpinnen et al 2012 Double blind, crossover RCT	N=30	Bite sensitive adults (aged 18 to 65 years) exposed to mosquito bites	Oral antihistamine (rupatadine)	Placebo	Skin reaction and pruritus

Abbreviations: n, number included in study; N, Number of people randomised; RCT, Randomised controlled trial; NSAID, Non-steroidal anti-inflammatory drugs.

[1] Not all people received all treatments (no further details on who received what treatments were reported)

[2] Cross-over design in 6 of the 7 RCTs

[3] No study designs reported observational study data only (7 single person case reports, 2 two-person case reports, 1 seventeen-person case series over 7-month period)

[4] Ages not reported

Table 2: Summary of included studies: antimicrobials

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Friedland et al 2012 NI RCT	N=19 (subgroup of 1,378 enrolled with an infected arthropod bite)	Patients aged 18 years and over with extensive cellulitis due to an infected arthropod bite	IV antibiotic (ceftaroline 600 mg BD for 5 to 14 days)	IV antibiotic (Vancomycin 1 g plus aztreonam 1g BD for 5 to 14 days)	Clinical response rate at day 3
Abbreviations: NI, Non inferiority; RCT, Randomised controlled trial; IV, Intravenous; BD, Twice daily.					

3 Evidence summary

Full details of the evidence are shown in appendix G: GRADE profiles.

The main results are summarised below for adults, young people and children with insect bites or stings.

See the summaries of product characteristics, British National Formulary (BNF) and BNF for children (BNFC) for information on drug interactions, contraindications, cautions and adverse effects of individual medicines, and for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding.

3.1 Antibiotics in adults

Antibiotic prescribing strategies in adults

No studies met the inclusion criteria.

Antibiotics in adults with an infected arthropod bite

Ceftaroline fosamil IV (cephalosporin) versus vancomycin with aztreonam IV (glycopeptide with a monobactam)

The evidence for cephalosporin versus glycopeptide with a monobactam for people with an insect bite or sting comes from a subgroup of people (n=19) with extensive cellulitis due to an infected arthropod bite (arthropod not defined) in a single RCT (Friedland et al 2012). The people in the subgroup were aged ≥18 years and were admitted to hospital, treated in an emergency department or urgent care setting, or were suitable for outpatient treatment with IV antibiotics. The intervention was intravenous ceftaroline fosamil 600 mg twice daily for 5 to 14 days compared with intravenous vancomycin 1 g with aztreonam 1 g twice daily for 5 to 14 days.

There is high uncertainty in the study results due to the small population size, being a subgroup of a larger study, only one effectiveness outcome was reported (clinical response at day 3 defined as cessation of infection spread and absence of fever ≤37.6°C) and no adverse effects data were reported.

Ceftaroline was not significantly different to vancomycin with aztreonam for clinical response at day 3 (1 RCT, n=19, 88.9% versus 60%, relative risk [RR] 1.48, 95% confidence interval [CI] 0.85 to 2.58; very low quality evidence).

No adverse effects were reported.

See GRADE table 7.

Antibiotic dosage, course length and route of administration in adults

No studies met the inclusion criteria.

Antihistamines in adults with an uninfected mosquito bite

The evidence for antihistamines in adults comes from 1 systematic review (Foex & Lee 2006) and 2 randomised controlled trials (RCTs) Karpinnen et al (2006) and Karpinnen et al (2012).

The systematic review contains 6 RCTs (including a 4 arm RCT) comparing an antihistamine (cetirizine [in 4 RCTs], ebastine [in 3 RCTs] or loratadine [in 1 RCT]) with placebo for mosquito-bites in adults. However, 2 RCTs and 1 arm of the 4 arm RCT were excluded from the NICE evidence review as the specific antihistamine (ebastine) is not available in the UK. Of the 4 included RCTs in the systematic review 3 were double-blind, cross-over design and 1 RCT was a double-blind RCT. Two additional crossover RCTs also compared an antihistamine (levocetirizine or rupatadine) with placebo for mosquito-bites in adults.

The population in the included RCTs from the systematic review varied and included healthy volunteers (2 RCTs) and adults with previous significant reactions to (1 RCT), or who were sensitive (1 RCTs) to, mosquito-bites. None of the participants had an infected mosquito bite. The population from the additional 2 RCTs was mosquito bite sensitive adults.

The setting of the studies was either in a laboratory (4 RCTs) where mosquitos were encouraged to bite in controlled conditions, or in a forest setting during the mosquito season (2 RCTs). The mosquito species also varied by study with *Anopheles stephensi* (a sub-tropical species) used in 1 RCT, *Aedes communis* (a species found in temperate regions) used in 2 RCTs and *Aedes aegypti* (found in tropical, subtropical and temperate regions throughout the world) used in 3 RCTs.

The treatments in each trial varied, as did the follow-up times and the washout periods (time between different treatments to allow the previous treatment to leave the body). However it is noted that the washout times used in the crossover RCTs were appropriate due to the short half-life of the interventions.

The main outcomes from the study were the size of the bite lesion (or wheal), which was measured in different ways in the studies, itchiness (pruritus) which was measured using visual analogue scales (although the scales varied by study) and adverse effects (usually sedation effects). Due to the study heterogeneity it was not possible to pool the outcome data. Follow-up was mostly from 15 minutes to 24 hours, only 1 RCT had longer duration of follow-up (daily follow-up to day 10). Studies varied as to whether they reported median or mean. No rationale was provided by the studies reporting median values which means results are unreliable and should be interpreted with caution.

Oral antihistamines versus placebo in adults with an uninfected mosquito bite

The evidence for antihistamines in adults for mosquito bites comes from a systematic review (Foex et al 2006) and 2 additional RCTs Karpinnen et al (2006) and Karpinnen et al (2012). In the systematic review 4 RCTs compared cetirizine 10 mg once daily (3 RCTs) or twice daily (1 RCT) with placebo and one RCT compared loratadine 10 mg once daily with placebo. In the additional 2 RCTs, 1 RCT compared levocetirizine 5 mg once daily with placebo and 1 RCT compared rupatadine 10 mg once daily with placebo.

Cetirizine 10 mg once or twice daily versus placebo

Bite lesion size

Three RCTs reported the outcome of mosquito bite lesion size at 15 minutes after bite exposure, although a therapeutic effect would not be expected within this time. In 2 RCTs, Cetirizine 10 mg once daily significantly reduced the median mosquito bite lesion size compared with placebo (1 RCT, n=27, median bite lesion size [IQR] 25 mm^2 [12 and 25 mm^2] for cetirizine versus 28 mm^2 [16 and 63 mm^2], p=0.003; low-quality evidence: 1 RCT, n=23, bite sizes and analysis not reported, states statistically significantly smaller with cetirizine but not placebo, p<0.01; low-quality evidence). In 1 other RCT, cetirizine 10 mg once daily was not significantly different to placebo for mosquito bite lesion size at 15 minutes after bite exposure (n=18, MD −4.20, 95% CI −9.72 to 1.32; very low quality evidence).

Cetirizine 10 mg once daily was not significantly different to placebo for mean mosquito bite lesion size at:

- 60 minutes after bite exposure in 2 RCTs (1 RCT, n=23, bite sizes and analysis not reported, states not significant; low-quality evidence: 1 RCT, n=18, 8.3±6.7 mm versus 11.7±10.5 mm, MD −3.40, 95% CI −9.15 to 2.35, very low quality evidence)
- 12 hours after bite exposure (1 RCT, n=18, 8.5±12.7 mm versus 13.7±19.8 mm, MD −5.20, 95% CI −16.07 to 5.67; very low quality evidence)
- 24 hours after bite exposure (1 RCT, n=18, 7.4±16.1 mm versus 12.6±21.9 mm, MD −5.20, 95% CI −17.76 to 7.36; very low quality evidence).

Cetirizine 10 mg twice daily was not significantly different to placebo for mean mosquito bite lesion size at:

- 10 minutes after bite exposure (1 RCT, n=9, mean difference [MD] −14.60, 95% confidence interval [CI] −51.02 to 21.82; very low-quality evidence)
- 12 to 24 hours (1 RCT, n=9, bite sizes and analysis not reported, states not significant, p=0.08; very low quality evidence) for delayed reaction mosquito bites.

Pruritus (itching)

Cetirizine 10 mg once daily significantly reduced:

- mean and median pruritus scores at 15 minutes after mosquito bite exposure in 3 RCTs compared to placebo (1 RCT, n=27, median visual analogue scale [VAS] 0, IQR 0 and 30 versus 50, IQR 10 and 70, p<0.001; very low quality evidence: 1 RCT, n=23, mean VAS scores not reported, p<0.01; very low quality evidence: 1 RCT, n=18, mean VAS ± standard deviation [SD] 11.2±13.2 versus 36.0±25.2, MD −24.80, 95% CI −37.94 to −11.66; very low quality evidence)
- mean pruritus scores at 60 minutes after mosquito bite exposure in 1 RCT compared to placebo (n=18, mean VAS±SD 9.8±12.7 versus 27.7±25.1, MD −17.90, 95% CI −30.9 to −4.90; very low quality evidence) but not in a second RCT (n=23, mean pruritus score and analysis not reported, states not significant; very low quality evidence)
- mean pruritus scores at 12 hours after mosquito bite exposure compared to placebo (1 RCT, n=18, mean VAS±SD 6.2±13.3 versus 18.7±20.9, MD −12.5, 95% CI −23.94 to −1.06; very low quality evidence).

Cetirizine 10 mg once daily was not significantly different to placebo for mean pruritus scores at 24 hours after mosquito bite exposure (1 RCT, n=18, mean VAS±SD 6.6±14.8 versus 18.9±25.5, MD −12.30, 95% CI −25.92 to 1.32; very low quality evidence).

Cetirizine 10 mg twice daily was not significantly different to placebo for pruritus score (not stated whether mean or median) at:

- 10, 30 or 90 minutes after mosquito bite exposure (n=9, pruritus scores and analysis not reported, states not significant; very low quality evidence).
- day 2, 5 or days 7 to 10 after mosquito bite exposure (n=9, pruritus core and analysis not reported, states not significant; very low quality evidence).

Cetirizine 10 mg twice daily significantly reduced pruritus compared with placebo (pruritus VAS score not stated whether mean or median) at:

- days 3 and 4 after mosquito bite exposure (n=9, pruritus scores and analysis not reported, day 3 $p<0.01$, day 4 $p<0.05$; very low quality evidence).
- at day 6 after mosquito bite exposure (n=9, pruritus scores and analysis not reported, $p<0.05$; very low quality evidence).

Adverse effects

Cetirizine 10 mg once daily was not significantly different to placebo for adverse effects (mild to severe sedation and headache, emesis or arthralgia), follow-up time point unclear (3 RCTs, n=66, 23% versus 10.6%, relative risk (RR) 2.17, 95% CI 0.95 to 4.94; very low-quality evidence; 1 RCT, n=27, 11.1% versus 14.8%, RR 0.75, 95% CI 0.19 to 3.04; very low-quality evidence).

One additional RCT comparing cetirizine 10 mg twice daily with placebo reported that rescue medicines (not defined) were used by 4 participants in the placebo group. Transient drowsiness was reported by 1 participant in the cetirizine group and 1 participant in the placebo group reported drowsiness and dry mouth.

Patient preference

Cetirizine 10 mg twice daily was preferred by 7 of 9 participants for mosquito bites, 1 participant preferred placebo and 1 participant had no preference in 1 RCT (n=9, no analysis reported).

See GRADE table 8.

Levocetirizine 5 mg once daily versus placebo

Bite lesion size

Compared to placebo, levocetirizine 5 mg once daily significantly reduced:

- median wheal (mosquito bite lesion) size at 15 minutes after bite exposure (1 RCT, n=28, median wheal size [IQR] 27 mm^2 [20 and 40 mm^2] versus 68 mm^2 [34 and 104 mm^2], 60% reduction in median wheal size $p<0.001$; very low quality evidence).
- median mosquito bite lesions size at 24 hours after bite exposure (1 RCT, n=8, median [IQR] 71 mm^2 [0 and 460 mm^2] versus 240 mm^2 [28 to 690 mm^2], 71% reduction in median bite lesion size $p=0.008$; very low quality evidence).

No rationale was provided as to why median values were reported, therefore results are unreliable and should be interpreted with caution.

Pruritus outcome

Compared to placebo, levocetirizine 5 mg once daily significantly reduced:

- median pruritus scores at 15 minutes after mosquito bite exposure (1 RCT, n=28, median VAS [IQR] 3 [1 and 5] versus 8 [7 and 9], 62% reduction in median VAS p<0.001; very low quality evidence).
- median pruritus scores from delayed bite lesions at 24 hours after mosquito bite exposure (1 RCT, n=8, mean VAS [range] 2.0 [0 and 6] versus 4.75 [2 and 8], 56% reduction in mean VAS pruritus score p=0.016; very low quality evidence).

Adverse effects

Levocetirizine 5 mg once daily was not significantly different to placebo for adverse effects (mild to moderate somnolence), follow-up period not defined (1 RCT, n=28, 17.9% versus 7.1%, RR 2.50, 95% CI 0.53 to 11.82; very low-quality evidence).

See GRADE table 9.

Loratadine 10 mg once daily versus placebo

Bite lesion size

Loratadine 10 mg once daily was not significantly different to placebo for median bite lesion size at 15 minutes after mosquito bite exposure (1 RCT, n=27, median [IQR] 25 mm^2 [16 and 48 mm^2] versus 28 mm^2 [16 and 63 mm^2], no analysis effect size reported p=0.09; very low quality evidence).

Pruritus (itching)

Loratadine 10 mg once daily was not significantly different to placebo for median pruritus score at 15 minutes after mosquito bite exposure (1 RCT, n=27, median [IQR] 30 [10 and 60] versus 50 [10 and 70], no analysis effect size reported p=0.067; very low quality evidence).

Adverse effects

Loratadine 10 mg once daily was not significantly different to placebo for adverse effects (mild to moderate sedation) at unclear follow-up time point (1 RCT, n=27, 18.5% versus 14.8%, RR 1.25, 95% CI 0.38 to 4.16; very low-quality evidence).

See GRADE table 10.

Rupatadine 10 mg once daily versus placebo

Bite lesion size

Rupatadine 10 mg once daily significantly reduced median bite lesion (wheal) size compared with placebo at 15 minutes after mosquito bite exposure (1 RCT, n=26, median 55 mm^2 versus 106 mm^2, 48% reduction p<0.001; very low quality evidence).

Rupatadine 10 mg once daily was not significantly different to placebo for delayed bite lesion size:

- at 24 hours after mosquito bite exposure (1 RCT, n=26, median 10.5 mm^2 versus 23mm^2, 54% reduction in bite lesion size, analysis not reported states non-significant; low-quality evidence)
- in reactive adults at 24 hours after mosquito bite exposure (1 RCT, n=20, unclear if mean or median bite size, 13.5 mm2 versus 33 mm2, 60% reduction in bite lesion size, analysis states non-significant; very low quality evidence).

Pruritus (itching)

Rupatadine 10 mg once daily significantly reduced median pruritus scores 15 minutes after mosquito bite exposure compared with placebo (1 RCT, n=26, median VAS score 47.5 mm^2 versus 60 mm^2, 21% reduction in median VAS for pruritus $p<0.05$; very low quality evidence) but was not significant for delayed bite reaction pruritus at 24 hours (no analysis reported).

Adverse effects

Rupatadine 10 mg once daily significantly increased adverse effects (sedation) compared with placebo, follow-up time point unclear (1 RCT, n=26, 30.8% versus 3.8%, RR 8.00, 95% CI 1.08 to 59.50; very low-quality evidence).

See GRADE table 11.

3.3 Antibiotics in children

No studies met the inclusion criteria.

3.4 Antihistamines in children with an uninfected mosquito bite

The evidence for antihistamines in children for mosquito bites (uninfected) comes from 1 double blind crossover randomised controlled trial included in a systematic review (Foex et al 2006). The study compared loratadine (0.3 mg/Kg) for 4 days with placebo for 4 days, after a 3 day washout period, in 28 children aged 2 to 11 years who were sensitive to mosquito bites (3 children dropped out of the RCT results are reported for 25 children, but only 12 children could evaluate pruritus on a visual analogue scale [VAS]). The study was conducted in a laboratory setting.

Loratadine (0.3 mg/Kg) once daily versus placebo for children with mosquito bites

Bite lesion size

Loratadine 0.3 mg/Kg once daily significantly reduced bite lesion size compared with placebo (1 RCT, n=25, median bite lesion size 35 mm^2 (range 6 to 120 mm^2) versus 64 mm^2 (range 9 to 400 mm^2), reported 45% reduction, $p<0.001$; low quality evidence) at 15 minutes after bite exposure but not at 2 hours (p=0.53; very low quality evidence) or 6 hours (p=0.14; low-quality evidence) after bite exposure.

Loratadine 0.3 mg/Kg once daily significantly reduced bite lesion size compared with placebo at 24 hours after bite exposure (1 RCT, n=25, median bite lesion size 36 mm^2 (range 0 to 1600 mm^2) versus 49 mm^2 (range 16 to 2500 mm^2), reported 27% reduction, p=0.004; very low quality evidence).

Pruritus (itching)

Loratadine 0.3 mg/Kg once daily significantly reduced pruritus compared with placebo at 15 minutes after bite exposure (1 RCT, n=12, median VAS 10, range 0 to 75 versus 45, range 0 to 90, reported 78% reduction, p=0.011; very low quality evidence).

Adverse effects

Loratadine 0.3 mg/Kg once daily was not significantly different to placebo for adverse effects (mild gastrointestinal pain and diarrhoea) follow-up time point not defined (1 RCT, n=25, 8% versus 0%, RR 5.00, 95% CI 0.25 to 99.16; very low-quality evidence).

See GRADE table 12.

Treatments for people with an uninfected brown recluse spider bite

The evidence for the treatment of brown recluse spider bites comes from 1 retrospective single centre study (Dyachenko and Rozenman 2006) of 52 people with presumed or definite brown recluse spider bite. Inclusion criteria was a characteristic skin lesion present in the 2 to 3 days after a bite. The study population had a mean age of 30.1 years (standard deviation ±13.6 years; range 9 to 66 years but only 4% of bites were in people aged under 12 years), with a 50% male to female ratio. Most participants (67.3%) of the study lived in rural areas of Israel.

Comorbidities were found in half of the participants (obesity was most common 28.8%; diabetes 9.6%; hypertension 9.6%; Non-Hodgkin's lymphoma 1.9%). Bites were most common in the evening or at night (75%) between April and August (spring and summer months). The most common location of bite was the thigh (48%), arm (19.2%) and abdomen (19.2%). Bites mostly occurred while sleeping or dressing (63.5%). The time interval between bite and presentation to hospital was after more than 24 hours in most cases (65%). Nine participants (17.3%) had severe lesions (grade 3 – extensive erythema, oedema, bulla, ulcer, skin necrosis >1 cm^2); 43 participants (82.7%) had moderate lesions (grade 2 – erythema, oedema, vesicle, skin necrosis <1 cm^2) and none (0%) had mild lesions (grade 1 – mild erythema, mild oedema, no necrosis) it is unclear if this severity scale was validated.

All patients were given prophylactic antibiotics (92.3% had cefalexin; no further details about dosage, course length or route of administration were reported), rest, cold compression and elevation. Most patients (92.3%) were given prednisolone (a corticosteroid) and an antihistamine (no further details reported), and a non-steroidal anti-inflammatory drug (NSAID) was given to 21 participants (40.4%; no further details reported).

Prophylactic antibiotics, rest, cold compression and elevation, corticosteroids, antihistamines and non-steroidal anti-inflammatory drugs

Study treatment (prophylactic antibiotics, rest, cold compression and elevation, corticosteroid, antihistamine and NSAID) did not prevent participants from developing necrotic lesions (1 observational study, n=52, 100% developed necrotic lesions; very low-quality evidence).

It was unclear if study treatment had an effect on time to healing. This was reported as 14 days to >8 weeks (mean 4.8 weeks). However, average time to healing was longer for people with more severe lesions; grade 3 lesions took 82 days and grade 2 lesions 38 days to heal (very low-quality evidence).

It was unclear if study treatment had an effect on time to length of hospital stay. Fifty seven percent of participants were hospitalised for >2 days, with those with grade 3 lesions on the thigh having significantly longer hospital stays ($p<0.02$; very low-quality evidence).

See GRADE table 13.

4 Terms used in the guideline

Insect bite or sting

For the purpose of this guideline, ‘insect bites’ also includes bites from spiders and ticks. Insects may bite with their mouthparts when feeding or defending themselves. Stings come from bees, wasps and hornets and are used only for defence.

Insect bite lesion

A bite lesion or wheal is the mark on the skin left following an insect bite.

Appendices

Appendix A: Evidence sources

Key area	Key question(s)	Evidence sources
Background	• What is the natural history of the infection? • What is the expected duration and severity of symptoms with or without antimicrobial treatment? • What are the most likely causative organisms? • What are the usual symptoms and signs of the infection? • What are the known complication rates of the infection, with and without antimicrobial treatment? • Are there any diagnostic or prognostic factors to identify people who may or may not benefit from an antimicrobial?	• No natural history data was found in the evidence review • Anderson et al 2019 • Drugs and Therapeutics Bulletin 2012 • Elliot et al 2006 • NHS 2016 • NICE CKS – insect bites and stings 2016 • NICE guideline CG134 Anaphylaxis (2011) • NICE guideline NG95 Lyme disease (2018)
Safety information	• What safety netting advice is needed for managing the infection? • What symptoms and signs suggest a more serious illness or condition (red flags)?	• Committee experience • BNF, July 2019 • NICE guideline CG183 drug allergy: diagnosis and management (2014) • NINICE guideline NG63: NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017)
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection • What is the need for broad or narrow spectrum antimicrobials? • What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	• NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • Chief medical officer (CMO) report (2011) • ESPAUR report (2016) • ESPAUR report (2017)

Key area	Key question(s)	Evidence sources
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• NHSBSA Drug Tariff
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)
Regulatory status	• What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics
Antimicrobial prescribing strategies	• What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review – see appendix F for included studies
Antimicrobials	• Which people are most likely to benefit from an antimicrobial?	• Evidence review – see appendix F for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second- and third-line treatment, including people with drug allergy)?	• Evidence review – see appendix F for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review – see appendix F for included studies • British National Formulary (BNF) July 2018 • BNF for children (BNFC) July 2018 • Summary of product characteristics

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Appendix B: Review protocol

Review question	What antimicrobial and non-antimicrobial interventions are effective in managing insect bites and stings?
Types of review question	Intervention
Objective of the review	To determine the effectiveness of prescribing interventions in managing infections caused by bites from insects to address antimicrobial resistance. In line with themajor goals of antimicrobial stewardship this includes interventions that lead prescribers to: • optimise therapy for individuals • reduce overuse, misuse or abuse of antimicrobials All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.
Eligibility criteria – population/disease/ condition/ issue/ domain	Adults and children (aged 72 hours and older) who have received an insect bite and/or sting of any severity.
Eligibility criteria – intervention(s)/ exposure(s) / prognostic factor(s)	The review will include studies which include: • Non-antimicrobial pharmacological interventions[1]. • Antimicrobial pharmacological interventions[2]. For the treatment of insects bites in primary, secondary or other care settings (for example outpatient parenteral antimicrobial therapy, walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example patient group direction).
Eligibility criteria – comparator(s)/ control or reference (gold) standard	Any other plausible strategy or comparator, including: • Placebo or no treatment. • Non-pharmacological interventions. • Non-antimicrobial pharmacological interventions. • Other antimicrobial pharmacological interventions.
Outcomes and prioritisation	a) infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) b) time to clinical cure (mean or median time to resolution of illness) c) reduction in symptoms (duration or severity) d) rate of complications with or without treatment

1 Non-antimicrobial pharmacological interventions include: antihistamines,analgesics and corticosteroids

2 Antimicrobial pharmacological interventions include: antibiotics, which could include back-up prescribing, standby or rescue therapy, narrow or broad spectrum, single, dual or triple therapy; and topical antiseptics

	e) Safety, tolerability, and adverse effects. f) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. g) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. h) Service user experience. i) Health and social care related quality of life. j) Health and social care utilisation (including length of stay, ITU stays, planned and unplanned contacts). The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).
Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If no systematic reviews or RCT evidence is available progress to: • Controlled trials • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Observational and cohort studies • Pre and post intervention studies (before and after) • Time series studies
Other inclusion exclusion criteria	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts • in relation to antimicrobial resistance, non-UK papers • antimicrobials that are not available in the UK • non-pharmacological interventions.
Proposed sensitivity/ sub-group analysis, or meta-regression	The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). These will be analysed within these categories to enable the production of management recommendations.
Selection process – duplicate screening/ selection/ analysis	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved.

	If large numbers of papers are identified and included at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.
Data management (software)	Data management will be undertaken using EPPI-reviewer software. Any pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following sources will be searched : • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cochrane Database of Systematic Reviews (CDSR) via Wiley • Database of Abstracts of Effectiveness (DARE) via Wiley – legacy database, last updated April 2015 • Embase via Ovid • Health Technology Assessment (HTA) via Wiley • MEDLINE via Ovid • MEDLINE-in-Process (including Daily Update and Epub Ahead of Print) via **Ovid** The search strategy will be developed in MEDLINE and then adapted or translated as appropriate for the other sources, taking into account their size, search functionality and subject coverage. A summary of the proposed search strategy is given in the appendix below. Database functionality will be used, where available, to exclude: • non-English language papers • animal studies • editorials, letters, news items, case reports and commentaries • conference abstracts and posters • theses and dissertations • duplicates. Date limits will be applied to restrict the search results to: • studies published from 2000 to the present day The results will be downloaded in the following sets: • Systematic reviews and meta-analysis • Randomised controlled trials • Observational and comparative studies • Other results Duplicates will be removed using automated and manual processes. The de-duplicated file will be uploaded into EPPI-Reviewer for data screening. See Appendix for details of search terms to be used.
Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-ng10050/consultation/html-content Email: infections@nice.org.uk
Highlight if amendment to previous protocol	For details please see the interim process guide (2017).

Search strategy – for one database	For details see appendix C.
Data collection process – forms/duplicate	GRADE profiles will be used, for details see appendix H.
Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix H.
Methods for assessing bias at outcome/ study level	Standard study checklists were used to critically appraise individual studies. For details please see the interim process guide (2017). The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see the interim process guide (2017).
Methods for analysis – combining studies and exploring (in)consistency	For details please see the interim process guide (2017).
Meta-bias assessment – publication bias, selective reporting bias	For details please see the interim process guide (2017).
Assessment of confidence in cumulative evidence	For details please see the interim process guide (2017).
Rationale/ context – Current management	For details please see the interim process guide (2017).

Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the interim process guide (2017). Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	Developed and funded by NICE.
Name of sponsor	Developed and funded by NICE.
Roles of sponsor	NICE funds and develops guidelines for those working in the NHS, public health, and social care in England.

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Appendix C: Literature search strategy

Database name: MEDLINE

1 "Insect Bites and Stings"/ (5820)

2 spider bites/ (1235)

3 exp Spider Venoms/ (2675)

4 Ceratopogonidae/ (1916)

5 Diptera/ (16114)

6 Culicidae/ (12129)

7 Nematocera/ (14)

8 Bedbugs/ (659)

9 wasps/ (4955)

10 Wasp Venoms/ (1790)

11 bees/ (11311)

12 exp bee venoms/ (5399)

13 ants/ (5307)

14 Ant Venoms/ (298)

15 Coleoptera/ (12888)

16 Siphonaptera/ (3367)

17 ((bite or bites or bitten* or biting* or sting* or stung* or venom* or toxic* or toxin* or infest*) adj3 (Insect* or Spider* or Araneid* or Arachnid* or Ceratopogonidae* or midge* or Diptera* or Tabanidae or horsefl* or horse-fl* or Culicidae* or mosquito* or Nematocera* or gnat* or Bedbug* or "bed bug*" or Cimicidae* or bug or bugs or Cimex* or Wasp* or Hornet* or Hymenopterous or Hymenoptera* or Bee or Bees or Vespid* or Apoidea* or Apidae* or ant or ants or ladybird* or lady-bird* or "lady bird*" or ladybug* or lady-bug* or "lady bug*" or Coleoptera or flea or fleas or Siphonaptera)).ti,ab. (17973)

18 ((wound* or infect* or injury* or injuries* or penetrat* or lesion* or tear* or shear* or punctur* or soft tissue* or bacteria* or bacterium) adj3 (Insect* or Spider* or Araneid* or Arachnid* or Ceratopogonidae* or midge* or Diptera* or Tabanidae or horsefl* or horse-fl* or Culicidae* or mosquito* or Nematocera* or gnat* or Bedbug* or "bed bug*" or Cimicidae* or bug or bugs or Cimex* or Wasp* or Hornet* or Hymenopterous or Hymenoptera* or Bee or Bees or Vespid* or Apoidea* or Apidae* or ant or ants or ladybird* or lady-bird* or "lady bird*" or ladybug* or lady-bug* or "lady bug*" or Coleoptera or flea or fleas or Siphonaptera)).ti,ab. (11555)

19 or/1-18 (95436)

20 Amikacin/ (3945)

21 Amikacin*.ti,ab. (8835)

22 exp Amoxicillin/ (10688)

23 Amoxicillin*.ti,ab. (13725)

24 Ampicillin/ (13184)

25 Ampicillin*.ti,ab. (21777)

26 Azithromycin/ (4658)

27 (Azithromycin* or Azithromicin* or Zithromax*).ti,ab. (7345)

28 Penicillin G/ (8965)

29 (Benzylpenicillin* or "Penicillin G").ti,ab. (8048)

30 (Ceftaroline* or Zinforo*).ti,ab. (590)

31 Clarithromycin/ (5951)

32 (Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab. (8523)

33 Chloramphenicol/ (19156)

34 (Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab. (25831)

35 Clindamycin/ (5500)

36 (Clindamycin* or Dalacin* or Zindaclin*).ti,ab. (9820)

37 Amoxicillin-Potassium Clavulanate Combination/ (2426)

38 (Co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab. (14801)

39 Doxycycline/ (9082)

40 (Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab. (12365)

41 (Ertapenem* or Invanz*).ti,ab. (1342)

42 Erythromycin/ (13554)

43 Erythromycin Estolate/ (148)

44 Erythromycin Ethylsuccinate/ (514)

45 (Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab. (20114)

46 Floxacillin/ (705)

47 (Floxacillin* or Flucloxacillin*).ti,ab. (812)

48 Framycetin/ (496)

49 Framycetin*.ti,ab. (161)

50 Fusidic Acid/ (1564)

51 ("Fusidic acid" or fusidate* or Fucidin*).ti,ab. (1970)

52 Gentamicins/ (17767)

53 (Gentamicin* or Gentamycin* or Cidomycin*).ti,ab. (25559)

54 Imipenem/ (3890)

55 (Imipenem* or Primaxin*).ti,ab. (9750)

56 Levamisole/ (4251)

57 (Levamisole* or ergamisol*).ti,ab. (4440)

58 Levofloxacin/ (3026)

59 (Levofloxacin* or Evoxil* or Tavanic*).ti,ab. (6889)

60 Linezolid/ (2686)

61 (Linezolid* or Zyvox*).ti,ab. (5189)
62 Meropenem*.ti,ab. (5630)
63 Metronidazole/ (12230)
64 Metronidazole*.ti,ab. (14516)
65 exp Neomycin/ (9083)
66 (neom?cin* or "Neo-Fradin").ti,ab. (9293)
67 Mupirocin/ (1152)
68 (Mupirocin* or Bactroban*).ti,ab. (1673)
69 Ofloxacin/ (5912)
70 (Ofloxacin* or Tarivid*).ti,ab. (6580)
71 Penicillin V/ (2151)
72 (Phenoxymethylpenicillin* or "Penicillin V").ti,ab. (1507)
73 Piperacillin/ (2640)
74 (Piperacillin* or Tazobactam* or Tazocin*).ti,ab. (6934)
75 Teicoplanin/ (2175)
76 (Teicoplanin* or Targocid*).ti,ab. (3418)
77 Tedizolid*.ti,ab. (216)
78 (Tigecycline* or Tygacil*).ti,ab. (2755)
79 Vancomycin/ (12824)
80 (Vancomycin* or Vancomicin* or Vancocin*).ti,ab. (24995)
81 or/20-80 (247572)
82 19 and 81 (453)
83 exp Aminoglycosides/ (148782)
84 Aminoglycoside*.ti,ab. (17821)
85 exp Penicillins/ (78500)
86 Penicillin*.ti,ab. (52848)
87 exp beta-Lactamases/ (21433)
88 exp beta-Lactamase inhibitors/ (7354)
89 ((beta adj Lactamase*) or betaLactamase* or beta-Lactamase*).ti,ab. (25701)
90 beta-Lactams/ (6165)
91 (beta-Lactam or betaLactam or beta Lactam or beta-Lactams or betaLactams or beta Lactams).ti,ab. (19880)
92 exp Carbapenems/ (9884)
93 Carbapenem*.ti,ab. (12145)
94 exp Cephalosporins/ (40734)
95 Cephalosporin*.ti,ab. (20854)
96 exp Fluoroquinolones/ (30691)
97 Fluoroquinolone*.ti,ab. (15081)
98 exp Macrolides/ (103450)

99 macrolide*.ti,ab. (14746)
100 Polymyxins/ (2844)
101 Polymyxin*.ti,ab. (6760)
102 exp Quinolones/ (44052)
103 Quinolone*.ti,ab. (13119)
104 exp Tetracyclines/ (46263)
105 Tetracycline*.ti,ab. (33911)
106 or/83-105 (494047)
107 19 and 106 (1250)
108 Chlorhexidine/ (7742)
109 (Chlorhexidine* or Unisept* or Hibiscrub* or Hydrex* or Hibi or HiBiTane*).ti,ab. (9787)
110 ("Dialkylcarbamoyl chloride" or "Cutimed Sorbact").ti,ab. (18)
111 Glucose oxidase/ (4760)
112 "Glucose oxidase".ti,ab. (5883)
113 Hydrogen Peroxide/ (53599)
114 ("Hydrogen peroxide" or crystacide*).ti,ab. (48657)
115 Lactoperoxidase/ (1308)
116 (Lactoperoxidase* or Flaminal*).ti,ab. (2392)
117 (Octenidine* or Octenilin*).ti,ab. (246)
118 (Polihexanide* or Suprasorb* or Polyhexamethylene*).ti,ab. (507)
119 Povidone-Iodine/ (2656)
120 (Povidone-Iodine* or Betadine* or Videne* or Inadine*).ti,ab. (3165)
121 Potassium Permanganate/ (1524)
122 ("Potassium permanganate" or "EN-Potab" or Permitabs).ti,ab. (1575)
123 Proflavine/ (523)
124 Proflavine*.ti,ab. (638)
125 Silver Sulfadiazine/ (902)
126 (Silver Sulfadiazine* or Flamazine*).ti,ab. (911)
127 (reactive oxygen or surgihoney*).ti,ab. (105351)
128 Iodine/ (24454)
129 (Iodine* or Iodoflex* or Iodosorb* or Iodozyme* or Oxyzyme*).ti,ab. (45398)
130 Honey/ (3504)
131 Apitherapy/ (119)
132 (Apitherap* or L-Mesitran or MANUKApli or Medihoney* or Melladerm* or Mesitran*).ti,ab. (103)
133 (honey* adj3 (topical* or local* or ointment* or cream* or skin* or dermatolog* or lotion* or gel* or paste*)).ti,ab. (353)
134 exp anti-infective agents, local/ (217038)
135 (Antiseptic* or anti-septic* or anti septic* or anti-infective* or anti infective* or antiinfective* or microbicide*).ti,ab. (14021)

136 Acetic Acid/ (9503)

137 (vinegar* or acetic acid*).ti,ab. (38674)

138 Sodium Bicarbonate/ (4383)

139 ((bicarbonate* or baking*) adj2 (sodium* or soda*)).ti,ab. (6347)

140 (S-Bicarb* or SodiBic* or Thamicarb* or Polyfusor* or EssCarb*).ti,ab. (4)

141 ((alkaliser* or alkalizer* or alkalinisation* or alkalinization* or alkalinising or alkalinizing) adj3 (drug* or agent* or therap*)).ti,ab. (202)

142 Magnesium Sulfate/ (4922)

143 ((Magnesium* or Epsom*) adj2 (sulfate* or sulphate* or salt*)).ti,ab. (5782)

144 or/108-143 (440533)

145 19 and 144 (1602)

146 analgesics/ (45922)

147 exp analgesics, non-narcotic/ (312935)

148 analgesics, short-acting/ (9)

149 antipyretics/ (2567)

150 (analgesic* or antipyretic*).ti,ab. (77679)

151 Acetaminophen/ (16938)

152 (paracetamol* or acetaminophen* or Panadol* or perfalgan* or calpol*).ti,ab. (22814)

153 Adrenal Cortex Hormones/ (61491)

154 (Corticosteroid* or corticoid* or Adrenal Cortex Hormone*).ti,ab. (100797)

155 Hydrocortisone/ (69477)

156 (Hydrocortisone* or Dioderm* or Lipocream* or Zenoxone*).ti,ab. (15722)

157 exp Prednisolone/ (49149)

158 (Prednisolone* or Fluprednisolone* or Methylprednisolone* or Deltacortril* or Dilacort* or Pevanti* or Deltastab* or Predsol*).ti,ab. (37648)

159 Anti-Inflammatory Agents, Non-Steroidal/ (63416)

160 nsaid*.ti,ab. (23024)

161 ((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).ti,ab. (36508)

162 Ibuprofen/ (8239)

163 (ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).ti,ab. (12330)

164 or/146-163 (658211)

165 19 and 164 (1266)

166 watchful waiting/ (2941)

167 "no intervention*".ti,ab. (7022)

168 (watchful* adj2 wait*).ti,ab. (2344)

169 (wait adj2 see).ti,ab. (1336)

170 (expectant* adj2 manage*).ti,ab. (2971)

171 (active* adj2 surveillance*).ti,ab. (6956)

172 (observing or observe or observes or observation or observations).ti,ab. (740365)

173 or/166-172 (761075)

174 19 and 173 (3404)

175 exp Histamine Antagonists/ (60276)

176 (histamin* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab. (8627)

177 Diphenhydramine/ (3863)

178 (Diphenhydramine* or Acrivastine* or Benadryl*).ti,ab. (3832)

179 Trimeprazine/ (319)

180 (Trimeprazine* or Alimemazine*).ti,ab. (253)

181 (Bilastine* or Ilaxten*).ti,ab. (83)

182 Cetirizine/ (1276)

183 (Cetirizine* or Piriteze* or Ziralton* or Zirtek* or Allacan* or Becoallergy*).ti,ab. (1422)

184 Chlorphenamine/ (1907)

185 (Chlorphenamine* or Allerief* or Piriton*).ti,ab. (89)

186 Cyclizine/ (271)

187 Cyclizine*.ti,ab. (204)

188 (Desloratadine* or Neoclarityn*).ti,ab. (518)

189 (Fexofenadine* or Telfast*).ti,ab. (812)

190 (Levocetirizine* or Xyzal*).ti,ab. (366)

191 Loratadine/ (1114)

192 (Loratadine* or Clarityn* or Lorapaed*).ti,ab. (1052)

193 (Mizolastine* or Mizollen*).ti,ab. (113)

194 Promethazine/ (2984)

195 (Promethazine* or Phenergan* or Sominex*).ti,ab. (2247)

196 Terfenadine/ (1557)

197 Terfenadine*.ti,ab. (1394)

198 or/175-197 (67158)

199 19 and 198 (393)

200 exp Antipruritics/ (26187)

201 (Antipruritic* or Anti-pruritic* or "Anti pruritic*").ti,ab. (789)

202 (Levomenthol* or Arjun* or Dermacool* or Menthoderm* or AquaSoothe*).ti,ab. (389)

203 (Crotamiton* or Eurax*).ti,ab. (124)

204 Calamine*.ti,ab. (81)

205 Anesthetics, Local/ (32490)

206 ((Anesthetic* or Anaesthetic* or Anesthesia* or Anaesthesia*) adj3 (topical* or local* or ointment* or cream* or skin* or dermatolog* or lotion* or gel* or paste*)).ti,ab. (45170)

207 or/200-206 (89737)

208 19 and 207 (232)

209 Inappropriate prescribing/ (2407)

210 ((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab. (29285)

211 ((prescription* or prescrib*) adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misuse* or "mis-us*" or overus* or "over-us*" or "over-prescri*" or abuse*)).ti,ab. (25623)

212 ((bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*") adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misus* or "mis-us*" or overus* or "over-us*" or "over-prescri*" or abuse*)).ti,ab. (106014)

213 or/209-212 (158504)

214 19 and 213 (533)

215 anti-infective agents/ or exp anti-bacterial agents/ (692324)

216 (antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*").ti,ab. (443415)

217 or/215-216 (892793)

218 19 and 217 (3365)

219 82 or 107 or 145 or 165 or 174 or 199 or 208 or 214 or 218 (10345)

220 limit 219 to yr="2000 -Current" (7152)

221 limit 220 to english language (6850)

222 limit 221 to (letter or historical article or comment or editorial or news) (132)

223 221 not 222 (6718)

224 Meta-Analysis.pt. (95140)

225 Meta-Analysis as Topic/ (16588)

226 Network Meta-Analysis/ (547)

227 Review.pt. (2462454)

228 exp Review Literature as Topic/ (10211)

229 (metaanaly* or metanaly* or (meta adj3 analy*)).ti,ab. (140434)

230 (review* or overview*).ti. (454759)

231 (systematic* adj5 (review* or overview*)).ti,ab. (146783)

232 ((quantitative* or qualitative*) adj5 (review* or overview*)).ti,ab. (9186)

233 ((studies or trial*) adj2 (review* or overview*)).ti,ab. (41893)

234 (integrat* adj3 (research or review* or literature)).ti,ab. (10712)

235 (pool* adj2 (analy* or data)).ti,ab. (26461)

236 (handsearch* or (hand adj3 search*)).ti,ab. (8554)

237 (manual* adj3 search*).ti,ab. (5522)

238 or/224-237 (2749982)

239 223 and 238 (524)
240 82 or 107 or 145 or 165 or 174 or 199 or 208 or 214 (8306)
241 limit 240 to yr="2000 -Current" (5637)
242 limit 241 to english language (5382)
243 limit 242 to (letter or historical article or comment or editorial or news) (108)
244 242 not 243 (5274)
245 Randomized Controlled Trial.pt. (472850)
246 Controlled Clinical Trial.pt. (92789)
247 Clinical Trial.pt. (513680)
248 exp Clinical Trials as Topic/ (319931)
249 Placebos/ (34164)
250 Random Allocation/ (96827)
251 Double-Blind Method/ (148625)
252 Single-Blind Method/ (25997)
253 Cross-Over Studies/ (44165)
254 ((random* or control* or clinical*) adj3 (trial* or stud*)).ti,ab. (1109443)
255 (random* adj3 allocat*).ti,ab. (32045)
256 placebo*.ti,ab. (200360)
257 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab. (160680)
258 (crossover* or (cross adj over*)).ti,ab. (80018)
259 or/245-258 (1860520)
260 244 and 259 (297)
261 Observational Studies as Topic/ (3448)
262 Observational Study/ (55507)
263 Epidemiologic Studies/ (7822)
264 exp Case-Control Studies/ (958939)
265 exp Cohort Studies/ (1805348)
266 Cross-Sectional Studies/ (280832)
267 Controlled Before-After Studies/ (365)
268 Historically Controlled Study/ (145)
269 Interrupted Time Series Analysis/ (510)
270 Comparative Study.pt. (1816449)
271 case control*.ti,ab. (115230)
272 case series.ti,ab. (62971)
273 (cohort adj (study or studies)).ti,ab. (166731)
274 cohort analy*.ti,ab. (6636)
275 (follow up adj (study or studies)).ti,ab. (46092)
276 (observational adj (study or studies)).ti,ab. (87284)
277 longitudinal.ti,ab. (214040)

278 prospective.ti,ab. (508197)
279 retrospective.ti,ab. (451120)
280 cross sectional.ti,ab. (295268)
281 or/261-280 (4272290)
282 244 and 281 (598)
283 239 or 260 or 282 (1278)
284 244 not 283 (4133)

****

a) Database name: Cochrane Library

Search Name: MCI - bites - insects

Date Run: 13/12/2018 10:58:10

Comment:

ID	Search	Hits
#1	MeSH descriptor: [Insect Bites and Stings] this term only	79
#2	MeSH descriptor: [Spider Bites] this term only	7
#3	MeSH descriptor: [Spider Venoms] explode all trees	6
#4	MeSH descriptor: [Ceratopogonidae] this term only	0
#5	MeSH descriptor: [Diptera] this term only	16
#6	MeSH descriptor: [Culicidae] this term only	45
#7	MeSH descriptor: [Nematocera] this term only	0
#8	MeSH descriptor: [Bedbugs] this term only	2
#9	MeSH descriptor: [Wasps] this term only	7
#10	MeSH descriptor: [Wasp Venoms] this term only	13
#11	MeSH descriptor: [Bees] this term only	17
#12	MeSH descriptor: [Bee Venoms] explode all trees	41
#13	MeSH descriptor: [Ants] this term only	8
#14	MeSH descriptor: [Ant Venoms] this term only	4
#15	MeSH descriptor: [Coleoptera] this term only	4
#16	MeSH descriptor: [Siphonaptera] this term only	6
#17	((bite or bites or bitten* or biting* or sting* or stung* or venom* or toxic* or toxin* or infest*) near/3 (Insect* or Spider* or Araneid* or Arachnid* or Ceratopogonidae* or midge* or Diptera* or Tabanidae or horsefl* or horse-fl* or Culicidae* or mosquito* or Nematocera* or gnat* or Bedbug* or "bed bug*" or Cimicidae* or bug or bugs or Cimex* or Wasp* or Hornet* or Hymenopterous or Hymenoptera* or Bee or Bees or Vespid* or Apoidea* or Apidae* or ant or ants or ladybird* or lady-bird* or "lady bird*" or ladybug* or lady-bug* or "lady bug*" or Coleoptera or flea or fleas or Siphonaptera)):ti,ab	415
#18	((wound* or infect* or injury* or injuries* or penetrat* or lesion* or tear* or shear* or punctur* or soft tissue* or bacteria* or bacterium) near/3 (Insect* or Spider* or Araneid* or Arachnid* or Ceratopogonidae* or midge* or Diptera* or Tabanidae or horsefl* or horse-fl* or Culicidae* or mosquito* or Nematocera* or gnat* or Bedbug* or "bed bug*" or Cimicidae* or bug or bugs or Cimex* or Wasp* or Hornet* or Hymenopterous or Hymenoptera* or Bee or Bees or Vespid* or Apoidea* or Apidae* or ant or ants or ladybird* or lady-bird* or "lady bird*" or ladybug* or lady-bug* or "lady bug*" or Coleoptera or flea or fleas or Siphonaptera)):ti,ab	203
#19	{OR #1-#18}	646
#20	[mh ^Amikacin]	355
#21	Amikacin*:ti,ab	707
#22	[mh Amoxicillin]	2580
#23	Amoxicillin*:ti,ab	3445
#24	[mh ^Ampicillin]	989

#25 Ampicillin*:ti,ab 1339

#26 [mh ^Azithromycin] 844

#27 (Azithromycin* OR Azithromicin* OR Zithromax*):ti,ab 1835

#28 [mh ^"Penicillin G"] 252

#29 (Benzylpenicillin* OR "Penicillin G"):ti,ab 349

#30 (Ceftaroline* OR Zinforo*):ti,ab 69

#31 [mh ^Clarithromycin] 1339

#32 (Clarithromycin* OR Clarie* OR Klaricid* OR Xetinin*):ti,ab 2371

#33 [mh ^Chloramphenicol] 286

#34 (Chloramphenicol* OR Cloranfenicol* OR Kemicetine* OR Kloramfenikol*):ti,ab 437

#35 [mh ^Clindamycin] 833

#36 (Clindamycin* OR Dalacin* OR Zindaclin*):ti,ab 1322

#37 [mh ^"Amoxicillin-Potassium Clavulanate Combination"] 573

#38 ((Co-amoxiclav*) OR Coamoxiclav* OR (Amox-clav*) OR (Amoxicillin-Clavulanic Acid*) OR (Amoxicillin-Potassium Clavulanate Combination*) OR (Amoxi-Clavulanate*) OR (Clavulanate Potentiated Amoxycillin Potassium*) OR (Clavulanate-Amoxicillin Combination*) OR Augmentin*):ti,ab 1457

#39 [mh ^Doxycycline] 968

#40 (Doxycycline* OR Efracea* OR Periostat* OR Vibramycin*):ti,ab 1472

#41 (Ertapenem* OR Invanz*):ti,ab 119

#42 [mh ^Erythromycin] 948

#43 [mh ^"Erythromycin Estolate"] 70

#44 [mh ^"Erythromycin Ethylsuccinate"] 87

#45 (Erythromycin* OR Erymax* OR Tiloryth* OR Erythrocin* OR Erythrolar* OR Erythroped*):ti,ab 1564

#46 [mh ^Floxacillin] 78

#47 (Floxacillin* OR Flucloxacillin*):ti,ab 135

#48 [mh ^Framycetin] 31

#49 Framycetin*:ti,ab 22

#50 [mh ^"Fusidic Acid"] 95

#51 ("Fusidic acid" OR fusidate* OR Fucidin*):ti,ab 183

#52 [mh ^Gentamicins] 1050

#53 (Gentamicin* OR Gentamycin* OR Cidomycin*):ti,ab 1637

#54 [mh ^Imipenem] 286

#55 (Imipenem* OR Primaxin*):ti,ab 506

#56 [mh ^Levamisole] 355

#57 (Levamisole* OR ergamisol*):ti,ab 603

#58 [mh ^Levofloxacin] 535

#59 (Levofloxacin* OR Evoxil* OR Tavanic*):ti,ab 1064

#60 [mh ^Linezolid] 180
#61 (Linezolid* OR Zyvox*):ti,ab 298
#62 Meropenem*:ti,ab 376
#63 [mh ^Metronidazole] 2109
#64 Metronidazole*:ti,ab 3356
#65 [mh Neomycin] 467
#66 (neom?cin* OR "Neo-Fradin"):ti,ab 395
#67 [mh ^Mupirocin] 194
#68 (Mupirocin* OR Bactroban*):ti,ab 363
#69 [mh ^Ofloxacin] 860
#70 (Ofloxacin* OR Tarivid*):ti,ab 884
#71 [mh ^"Penicillin V"] 308
#72 (Phenoxymethylpenicillin* OR "Penicillin V"):ti,ab 340
#73 [mh ^Piperacillin] 396
#74 (Piperacillin* OR Tazobactam* OR Tazocin*):ti,ab 703
#75 [mh ^Teicoplanin] 166
#76 (Teicoplanin* OR Targocid*):ti,ab 224
#77 Tedizolid*:ti,ab 46
#78 (Tigecycline* OR Tygacil*):ti,ab 101
#79 [mh ^Vancomycin] 665
#80 (Vancomycin* OR Vancomicin* OR Vancocin*):ti,ab 1317
#81 {OR #20-#80} 23298
#82 #19 and #81 11
#83 [mh Aminoglycosides] 8088
#84 Aminoglycoside*:ti,ab 665
#85 [mh Penicillins] 5297
#86 Penicillin*:ti,ab 2106
#87 [mh "beta-Lactamases"] 83
#88 [mh "beta-Lactamase inhibitors"] 85
#89 ((beta NEAR/1 Lactamase*) OR betaLactamase* OR (beta-Lactamase*)):ti,ab 538
#90 [mh ^"beta-Lactams"] 138
#91 ("beta-Lactam" OR betaLactam OR "beta Lactam" OR "beta-Lactams" OR betaLactams OR "beta Lactams"):ti,ab 543
#92 [mh Carbapenems] 499
#93 Carbapenem*:ti,ab 376
#94 [mh Cephalosporins] 4153
#95 Cephalosporin*:ti,ab 1194
#96 [mh Fluoroquinolones] 3247

#97 Fluoroquinolone*:ti,ab 792

#98 [mh Macrolides] 7887

#99 macrolide*:ti,ab 782

#100 [mh ^Polymyxins] 106

#101 Polymyxin*:ti,ab 298

#102 [mh Quinolones] 4456

#103 Quinolone*:ti,ab 524

#104 [mh Tetracyclines] 2295

#105 Tetracycline*:ti,ab 1569

#106 {OR #83-#105} 31147

#107 #19 and #106 18

#108 [mh ^Chlorhexidine] 1941

#109 (Chlorhexidine* OR Unisept* OR Hibiscrub* OR Hydrex* OR Hibi OR HiBiTane*):ti,ab 3089

#110 ("Dialkylcarbamoyl chloride" OR "Cutimed Sorbact"):ti,ab 6

#111 [mh ^"Glucose oxidase"] 35

#112 "Glucose oxidase":ti,ab 79

#113 [mh "Hydrogen Peroxide"] 546

#114 ("Hydrogen peroxide" OR crystacide*):ti,ab 694

#115 [mh ^Lactoperoxidase] 27

#116 (Lactoperoxidase* OR Flaminal*):ti,ab 32

#117 (Octenidine* OR Octenilin*):ti,ab 59

#118 (Polihexanide* OR Suprasorb* OR Polyhexamethylene*):ti,ab 84

#119 [mh ^"Povidone-Iodine"] 557

#120 ((Povidone-Iodine*) OR Betadine* OR Videne* OR Inadine*):ti,ab 715

#121 [mh ^"Potassium Permanganate"] 6

#122 ("Potassium permanganate" OR "EN-Potab" OR Permitabs):ti,ab 19

#123 [mh ^Proflavine] 14

#124 Proflavine*:ti,ab 12

#125 [mh ^" Silver Sulfadiazine"] 0

#126 ((Silver NEXT Sulfadiazine*) OR Flamazine*):ti,ab 188

#127 ("reactive oxygen" OR surgihoney*):ti,ab 1171

#128 [mh ^Iodine] 495

#129 (Iodine* OR Iodoflex* OR Iodosorb* OR Iodozyme* OR Oxyzyme*):ti,ab 2858

#130 [mh ^Honey] 143

#131 [mh ^Apitherapy] 18

#132 (Apitherap* or L-Mesitran or MANUKApli or Medihoney* or Melladerm* or Mesitran*):ti,ab 22

#133 (honey* near/3 (topical* or local* or ointment* or cream* or skin* or dermatolog* or lotion* or gel* or paste*)):ti,ab 83

#134 [mh "anti-infective agents, local"] 1996

#135 (Antiseptic* OR (anti-septic*) OR (anti NEXT septic*) OR (anti-infective*) OR (anti NEXT infective*) OR antiinfective* OR microbicide*):ti,ab 1622

#136 [mh ^"Acetic Acid"] 187

#137 (vinegar* OR (acetic NEXT acid*)):ti,ab 632

#138 [mh ^"Sodium Bicarbonate"] 611

#139 ((bicarbonate* or baking*) NEAR/2 (sodium* or soda*)):ti,ab 1118

#140 ((S-Bicarb*) OR SodiBic* OR Thamicarb* OR Polyfusor* OR EssCarb*):ti,ab 1

#141 ((alkaliser* OR alkalizer* OR alkalinisation* OR alkalinization* OR alkalinising OR alkalinizing) NEAR/3 (drug* OR agent* OR therap*)):ti,ab 19

#142 [mh ^"Magnesium Sulfate"] 821

#143 ((Magnesium* OR Epsom*) NEAR/2 (sulfate* OR sulphate* OR salt*)):ti,ab 1676

#144 {OR #108-#143} 13975

#145 #19 and #144 8

#146 [mh ^analgesics] 4499

#147 [mh "analgesics, non-narcotic"] 8668

#148 [mh ^"analgesics, short-acting"] 0

#149 [mh ^antipyretics] 62

#150 (analgesic* OR antipyretic*):ti,ab 24790

#151 [mh ^Acetaminophen] 2781

#152 (paracetamol* OR acetaminophen* OR Panadol* OR perfalgan* OR calpol*):ti,ab 6010

#153 [mh ^"Adrenal Cortex Hormones"] 2149

#154 (Corticosteroid* or corticoid* or Adrenal Cortex Hormone*):ti,ab 14862

#155 [mh ^Hydrocortisone] 5550

#156 (Hydrocortisone* or Dioderm* or Lipocream* or Zenoxone*):ti,ab 1865

#157 [mh Prednisolone] 4402

#158 (Prednisolone* OR Fluprednisolone* OR Methylprednisolone* OR Deltacortril* OR Dilacort* OR Pevanti* OR Deltastab* OR Predsol*):ti,ab 6258

#159 [mh ^"Anti-Inflammatory Agents, Non-Steroidal"] 6180

#160 nsaid*:ti,ab 4265

#161 ((nonsteroid* OR (non NEXT steroid*)) NEXT ((anti NEXT inflammator*) OR antiinflammator*)):ti,ab 5322

#162 [mh ^Ibuprofen] 1721

#163 (ibuprofen* OR arthrofen* OR ebufac* OR rimafen* OR brufen* OR calprofen* OR feverfen* OR nurofen* OR orbifen*):ti,ab 3177

#164 {OR #146-#163} 65912

#165 #19 and #164 22

#166 [mh ^"watchful waiting"] 258

#167 (no NEXT intervention*):ti,ab 3921

#168 (watchful* NEAR/2 wait*):ti,ab 415

#169 (wait NEAR/2 see):ti,ab 158

#170 (expectant* NEAR/2 manage*):ti,ab 640

#171 (active* NEAR/2 surveillance*):ti,ab 480

#172 (observing OR observe OR observes OR observation OR observations):ti,ab 49017

#173 {OR #166-#172} 54289

#174 #19 and #173 38

#175 [mh "histamine antagonists"] 2716

#176 (histamin* near/3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)):ti,ab 855

#177 [mh ^Diphenhydramine] 434

#178 (Diphenhydramine* or Acrivastine* or Benadryl*):ti,ab 666

#179 [mh ^Trimeprazine] 39

#180 (Trimeprazine* or Alimemazine*):ti,ab 47

#181 (Bilastine* or Ilaxten*):ti,ab 71

#182 [mh ^Cetirizine] 530

#183 (Cetirizine* or Piriteze* or Ziralton* or Zirtek* or Allacan* or Becoallergy*):ti,ab 777

#184 [mh ^Chlorphenamine] 262

#185 (Chlorphenamine* or Allerief* or Piriton*):ti,ab 24

#186 [mh ^Cyclizine] 36

#187 Cyclizine*:ti,ab 50

#188 (Desloratadine* or Neoclarityn*):ti,ab 346

#189 (Fexofenadine* or Telfast*):ti,ab 383

#190 (Levocetirizine* or Xyzal*):ti,ab 268

#191 [mh ^Loratadine] 447

#192 (Loratadine* or Clarityn* or Lorapaed*):ti,ab 586

#193 (Mizolastine* or Mizollen*):ti,ab 76

#194 [mh ^Promethazine] 356

#195 (Promethazine* or Phenergan* or Sominex*):ti,ab 440

#196 [mh ^Terfenadine] 535

#197 Terfenadine*:ti,ab 533

#198 {OR #175-#197} 6186

#199 #19 and #198 26

#200 [mh Antipruritics] 126

#201 (Antipruritic* or Anti-pruritic* or "Anti pruritic*"):ti,ab 216

#202 (Levomenthol* or Arjun* or Dermacool* or Menthoderm* or AquaSoothe*):ti,ab 29

#203 (Crotamiton* or Eurax*):ti,ab 23

#204 Calamine*:ti,ab 8

#205 [mh ^"Anesthetics, Local"] 7690

#206 ((Anesthetic* or Anaesthetic* or Anesthesia* or Anaesthesia*) near/3 (topical* or local* or ointment* or cream* or skin* or dermatolog* or lotion* or gel* or paste*)):ti,ab 11684

#207 {OR #200-#206} 16143

#208 #19 and #207 4

#209 [mh ^"Inappropriate prescribing"] 110

#210 ((delay* or defer*) near/3 (treat* or therap* or interven*)):ti,ab 4203

#211 ((prescription* OR prescrib*) NEAR/3 ("red flag" OR strateg* OR appropriat* OR inappropriat* OR unnecessary OR defer* OR delay* OR no OR non OR behaviour* OR behavior* OR optimal OR optimi* OR reduc* OR decreas* OR declin* OR rate* OR improv* OR (back-up*) OR backup* OR immediate* OR rapid* OR short* OR long* OR standby OR (stand by) OR rescue OR escalat* OR (de-escalat*) OR misuse* OR (mis-us*) OR overus* OR (over-us*) OR (over-prescri*) OR abuse*)):ti,ab 4293

#212 ((bacter* OR antibacter* OR (anti-bacter*) OR (anti NEXT bacter*) OR antimicrobial OR (anti-microbial) OR (anti NEXT microbial) OR antibiot* OR (anti-biot*) OR (anti NEXT biot*)) NEAR/3 ((red NEAR flag) OR strateg* OR appropriat* OR inappropriat* OR unnecessary OR defer* OR delay* OR no OR non OR behaviour* OR behavior* OR optimal OR optimi* OR reduc* OR decreas* OR declin* OR rate* OR improv* OR (back-up*) OR backup* OR immediate* OR rapid* OR short* OR long* OR standby OR (stand NEXT by) OR rescue OR escalat* OR (de-escalat*) OR misus* OR (mis-us*) OR overus* OR (over-us*) OR (over-prescri*) OR abuse*)):ti,ab 8390

#213 {OR #209-#212} 16327

#214 #19 and #213 7

#215 [mh ^"anti-infective agents"] or [mh "anti-bacterial agent"] 12912

#216 (antibacter* OR (anti-bacter*) OR (anti NEXT bacter*) OR antimicrobial OR "anti-microbial" OR "anti microbial" OR antibiot* OR (anti-biot*) OR (anti NEXT biot*)):ti,ab 24735

#217 {OR #215-#216} 30950

#218 #19 and #217 16

#219 #82 or #107 or #145 or #165 or #174 or #199 or #208 or #214 or #218 with Cochrane Library publication date Between Jan 2000 and Dec 2018, in Cochrane Reviews 12

#220 #82 or #107 or #145 or #165 or #174 or #199 or #208 or #214 or #218 with Cochrane Library publication date Between Jan 2000 and Dec 2018, in Trials 94

b) Database name: Embase

Database: Embase <1974 to 2018 December 10>

Search Strategy:

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1 "Insect Bites and Stings"/ (3225)

2 spider bites/ (1163)

3 exp Spider Venoms/ (2368)

4 Ceratopogonidae/ (1253)

5 Diptera/ (3335)

6 Culicidae/ (18002)

7 Nematocera/ (47)

8 Bedbugs/ (631)

9 wasps/ (4830)

10 Wasp Venoms/ (1311)

11 bees/ (6146)

12 exp bee venoms/ (3164)

13 ants/ (5336)

14 Ant Venoms/ (280)

15 Coleoptera/ (4588)

16 Siphonaptera/ (1742)

17 ((bite or bites or bitten* or biting* or sting* or stung* or venom* or toxic* or toxin* or infest*) adj3 (Insect* or Spider* or Araneid* or Arachnid* or Ceratopogonidae* or midge* or Diptera* or Tabanidae or horsefl* or horse-fl* or Culicidae* or mosquito* or Nematocera* or gnat* or Bedbug* or "bed bug*" or Cimicidae* or bug or bugs or Cimex* or Wasp* or Hornet* or Hymenopterous or Hymenoptera* or Bee or Bees or Vespid* or Apoidea* or Apidae* or ant or ants or ladybird* or lady-bird* or "lady bird*" or Coleoptera or flea or fleas or Siphonaptera)).ti,ab. (21228)

18 ((wound* or infect* or injury* or injuries* or penetrat* or lesion* or tear* or shear* or punctur* or soft tissue* or bacteria* or bacterium) adj3 (Insect* or Spider* or Araneid* or Arachnid* or Ceratopogonidae* or midge* or Diptera* or Tabanidae or horsefl* or horse-fl* or Culicidae* or mosquito* or Nematocera* or gnat* or Bedbug* or "bed bug*" or Cimicidae* or bug or bugs or Cimex* or Wasp* or Hornet* or Hymenopterous or Hymenoptera* or Bee or Bees or Vespid* or Apoidea* or Apidae* or ant or ants or ladybird* or lady-bird* or "lady bird*" or Coleoptera or flea or fleas or Siphonaptera)).ti,ab. (12452)

19 or/1-18 (74066)

20 Amikacin/ (42713)

21 Amikacin*.ti,ab. (12487)

22 exp Amoxicillin/ (58208)

23 Amoxicillin*.ti,ab. (20495)

24 Ampicillin/ (79530)

25 Ampicillin*.ti,ab. (26070)

26 Azithromycin/ (31529)

27 (Azithromycin* or Azithromicin* or Zithromax*).ti,ab. (11186)

28 Penicillin G/ (73316)

29 (Benzylpenicillin* or "Penicillin G").ti,ab. (8878)

30 ceftaroline/ (1143)

31 (Ceftaroline* or Zinforo*).ti,ab. (805)

32 Clarithromycin/ (34518)

33 (Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab. (12708)

34 Chloramphenicol/ (53937)

35 (Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab. (24101)

36 Clindamycin/ (47359)

37 (Clindamycin* or Dalacin* or Zindaclin*).ti,ab. (12738)

38 Amoxicillin-Potassium Clavulanate Combination/ (34924)

39 (Co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab. (19470)

40 Doxycycline/ (47976)

41 (Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab. (17318)

42 ertapenem/ (6276)

43 (Ertapenem* or Invanz*).ti,ab. (2152)

44 Erythromycin/ (68979)

45 Erythromycin Estolate/ (730)

46 Erythromycin Ethylsuccinate/ (1742)

47 (Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab. (23034)

48 Flucloxacillin/ (7920)

49 (Floxacillin* or Flucloxacillin*).ti,ab. (1303)

50 Framycetin/ (1374)

51 Framycetin*.ti,ab. (157)

52 Fusidic Acid/ (7170)

53 ("Fusidic acid" or fusidate* or Fucidin*).ti,ab. (2196)

54 Gentamicin/ (99056)

55 (Gentamicin* or Gentamycin* or Cidomycin*).ti,ab. (32233)

56 Imipenem/ (34707)

57 (Imipenem* or Primaxin*).ti,ab. (13993)

58 Levamisole/ (11620)

59 (Levamisole* or ergamisol*).ti,ab. (5389)

60 Levofloxacin/ (32069)

61 (Levofloxacin* or Evoxil* or Tavanic*).ti,ab. (10934)

62 Linezolid/ (18082)

63 (Linezolid* or Zyvox*).ti,ab. (7557)

64 meropenem/ (27579)

65 Meropenem*.ti,ab. (9242)

66 Metronidazole/ (62771)

67 Metronidazole*.ti,ab. (19883)

68 exp Neomycin/ (19442)

69 (neom?cin* or "Neo-Fradin").ti,ab. (9123)

70 pseudomonic acid/ (6435)

71 (Mupirocin* or Bactroban*).ti,ab. (2320)

72 Ofloxacin/ (24976)

73 (Ofloxacin* or Tarivid*).ti,ab. (8768)

74 Penicillin V/ (6886)

75 (Phenoxymethylpenicillin* or "Penicillin V").ti,ab. (1522)

76 Piperacillin/ (18521)

77 (Piperacillin* or Tazobactam* or Tazocin*).ti,ab. (11039)

78 Teicoplanin/ (12952)

79 (Teicoplanin* or Targocid*).ti,ab. (4735)

80 tedizolid/ (512)

81 Tedizolid*.ti,ab. (285)

82 tigecycline/ (8940)

83 (Tigecycline* or Tygacil*).ti,ab. (4064)

84 Vancomycin/ (81787)

85 (Vancomycin* or Vancomicin* or Vancocin*).ti,ab. (35146)

86 or/20-85 (559148)

87 19 and 86 (1340)

88 exp aminoglycoside antibiotic agent/ or exp aminoglycoside derivative/ (246233)

89 Aminoglycoside*.ti,ab. (21979)

90 exp penicillin derivative/ (271385)

91 Penicillin*.ti,ab. (50064)

92 exp beta-Lactamase inhibitor/ (71945)

93 (("beta Lactamase*" or betaLactamase*) adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab. (3697)

94 beta-Lactam/ or exp beta lactam antibiotic/ or exp beta lactam derivative/ (398312)

95 ("beta-Lactam" or betaLactam or "beta Lactam" or "beta-Lactams" or betaLactams or "beta Lactams").ti,ab. (25402)

96 exp carbapenem derivative/ (8261)

97 Carbapenem*.ti,ab. (16969)

98 exp cephalosporin derivative/ (209401)

99 Cephalosporin*.ti,ab. (27484)

100 exp quinolone derivative/ (154685)
101 Fluoroquinolone*.ti,ab. (19510)
102 exp Macrolide/ (204429)
103 macrolide*.ti,ab. (19245)
104 Polymyxin/ (5792)
105 Polymyxin*.ti,ab. (7053)
106 exp quinolone derivative/ (154685)
107 Quinolone*.ti,ab. (17696)
108 exp tetracycline derivative/ (147951)
109 Tetracycline*.ti,ab. (35895)
110 or/88-109 (776451)
111 19 and 110 (1906)
112 Chlorhexidine/ (15889)
113 (Chlorhexidine* or Unisept* or Hibiscrub* or Hydrex* or Hibi or HiBiTane*).ti,ab. (11255)
114 ("Dialkylcarbamoyl chloride" or "Cutimed Sorbact").ti,ab. (23)
115 Glucose oxidase/ (6470)
116 "Glucose oxidase".ti,ab. (6795)
117 Hydrogen Peroxide/ (83914)
118 ("Hydrogen peroxide" or crystacide*).ti,ab. (56061)
119 Lactoperoxidase/ (1631)
120 (Lactoperoxidase* or Flaminal*).ti,ab. (2557)
121 octenidine/ (539)
122 (Octenidine* or Octenilin*).ti,ab. (308)
123 "poly(hexamethylenebiguanide)"/ (796)
124 (Polihexanide* or Suprasorb* or Polyhexamethylene*).ti,ab. (635)
125 Povidone iodine/ (9500)
126 (Povidone-Iodine* or Betadine* or Videne* or Inadine*).ti,ab. (4011)
127 permanganate potassium/ (2826)
128 ("Potassium permanganate" or "EN-Potab" or Permitabs).ti,ab. (1790)
129 Proflavine/ (826)
130 Proflavine*.ti,ab. (484)
131 sulfadiazine silver/ (3657)
132 (Silver Sulfadiazine* or Flamazine*).ti,ab. (1174)
133 reactive oxygen metabolite/ (146097)
134 (reactive oxygen or surgihoney*).ti,ab. (129669)
135 Iodine/ (24854)
136 (Iodine* or Iodoflex* or Iodosorb* or Iodozyme* or Oxyzyme*).ti,ab. (51587)
137 honey-based wound dressing/ or honey/ (6104)

138 Apitherapy/ (184)

139 (Apitherap* or L-Mesitran or MANUKApli or Medihoney* or Melladerm* or Mesitran*).ti,ab. (140)

140 (honey* adj3 (topical* or local* or ointment* or cream* or skin* or dermatolog* or lotion* or gel* or paste*)).ti,ab. (451)

141 exp topical antiinfective agent/ (307426)

142 (Antiseptic* or anti-septic* or anti septic* or anti-infective* or anti infective* or antiinfective* or microbicide*).ti,ab. (17973)

143 vinegar/ (1321)

144 (vinegar* or acetic acid*).ti,ab. (47579)

145 Bicarbonate/ (44690)

146 ((bicarbonate* or baking*) adj2 (sodium* or soda*)).ti,ab. (8328)

147 (S-Bicarb* or SodiBic* or Thamicarb* or Polyfusor* or EssCarb*).ti,ab. (6)

148 ((alkaliser* or alkalizer* or alkalinisation* or alkalinization* or alkalinising or alkalinizing) adj3 (drug* or agent* or therap*)).ti,ab. (260)

149 Magnesium Sulfate/ (15039)

150 ((Magnesium* or Epsom*) adj2 (sulfate* or sulphate* or salt*)).ti,ab. (7542)

151 or/112-150 (639928)

152 19 and 151 (1621)

153 analgesic agent/ (81765)

154 exp analgesics, non-narcotic/ (828677)

155 short acting analgesic agent/ (34)

156 antipyretic agent/ (5469)

157 (analgesic* or antipyretic*).ti,ab. (108349)

158 paracetamol/ (83300)

159 (paracetamol* or acetaminophen* or Panadol* or perfalgan* or calpol*).ti,ab. (35397)

160 corticosteroid/ or corticosteroid therapy/ or corticosteroid derivative/ (240548)

161 (Corticosteroid* or corticoid* or Adrenal Cortex Hormone*).ti,ab. (141330)

162 Hydrocortisone/ (115745)

163 (Hydrocortisone* or Dioderm* or Lipocream* or Zenoxone*).ti,ab. (17662)

164 Prednisolone/ (115342)

165 (Prednisolone* or Fluprednisolone* or Methylprednisolone* or Deltacortril* or Dilacort* or Pevanti* or Deltastab* or Predsol*).ti,ab. (54918)

166 nonsteroid antiinflammatory agent/ (115351)

167 nsaid*.ti,ab. (39435)

168 ((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).ti,ab. (47665)

169 ibuprofen derivative/ or ibuprofen/ (46700)

170 (ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).ti,ab. (17379)

171 or/153-170 (1357994)

172 19 and 171 (2721)
173 watchful waiting/ (3589)
174 "no intervention*".ti,ab. (9789)
175 (watchful* adj2 wait*).ti,ab. (3500)
176 (wait adj2 see).ti,ab. (1869)
177 (expectant* adj2 manage*).ti,ab. (4428)
178 (active* adj2 surveillance*).ti,ab. (11283)
179 (observing or observe or observes or observation or observations).ti,ab. (862177)
180 or/173-179 (892522)
181 19 and 180 (2709)
182 exp antihistaminic agent/ (223993)
183 (histamin* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab. (10962)
184 Diphenhydramine/ (20280)
185 (Diphenhydramine* or Acrivastine* or Benadryl*).ti,ab. (4985)
186 Alimemazine/ (1378)
187 (Trimeprazine* or Alimemazine*).ti,ab. (248)
188 bilastine/ (207)
189 (Bilastine* or Ilaxten*).ti,ab. (148)
190 Cetirizine/ (7250)
191 (Cetirizine* or Piriteze* or Ziralton* or Zirtek* or Allacan* or Becoallergy*).ti,ab. (2285)
192 Chlorpheniramine/ (6978)
193 (Chlorphenamine* or Allerief* or Piriton*).ti,ab. (166)
194 Cyclizine/ (1388)
195 Cyclizine*.ti,ab. (247)
196 (Desloratadine* or Neoclarityn*).ti,ab. (785)
197 (Fexofenadine* or Telfast*).ti,ab. (1285)
198 (Levocetirizine* or Xyzal*).ti,ab. (636)
199 Loratadine/ (5747)
200 (Loratadine* or Clarityn* or Lorapaed*).ti,ab. (1552)
201 (Mizolastine* or Mizollen*).ti,ab. (204)
202 Promethazine/ (12650)
203 (Promethazine* or Phenergan* or Sominex*).ti,ab. (2577)
204 Terfenadine/ (6050)
205 Terfenadine*.ti,ab. (1801)
206 or/182-205 (227365)
207 19 and 206 (1632)
208 exp antipruritic agent/ (43074)
209 (Antipruritic* or Anti-pruritic* or "Anti pruritic*").ti,ab. (1111)

210 (Levomenthol* or Arjun* or Dermacool* or Menthoderm* or AquaSoothe*).ti,ab. (707)

211 (Crotamiton* or Eurax*).ti,ab. (160)

212 calamine/ (501)

213 Calamine*.ti,ab. (94)

214 local anesthetic agent/ (26622)

215 ((Anesthetic* or Anaesthetic* or Anesthesia* or Anaesthesia*) adj3 (topical* or local* or ointment* or cream* or skin* or dermatolog* or lotion* or gel* or paste*)).ti,ab. (57908)

216 or/208-215 (115153)

217 19 and 216 (273)

218 Inappropriate prescribing/ (3434)

219 ((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab. (43707)

220 ((prescription* or prescrib*) adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misuse* or "mis-us*" or overus* or "over-us*" or "over-prescri*" or abuse*)).ti,ab. (41532)

221 ((bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*") adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misus* or "mis-us*" or overus* or "over-us*" or "over-prescri*" or abuse*)).ti,ab. (133345)

222 or/218-221 (214906)

223 19 and 222 (530)

224 antiinfective agent/ (160687)

225 (antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*").ti,ab. (566447)

226 or/224-225 (636106)

227 19 and 226 (2373)

228 87 or 111 or 152 or 172 or 181 or 207 or 217 or 223 or 227 (10587)

229 limit 228 to yr="2000 -Current" (8484)

230 limit 229 to english language (8027)

231 (letter or editorial).pt. (1642662)

232 230 not 231 (7831)

233 (conference abstract or conference paper or conference proceeding or "conference review").pt. (3992679)

234 232 not 233 (6326)

235 limit 234 to medline (1925)

236 234 not 235 (4401)

237 Systematic Review/ (187944)

238 Meta Analysis/ (154125)

239 Review/ (2305205)
240 Review.pt. (2387135)
241 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (183929)
242 (review$ or overview$).ti. (517701)
243 (systematic$ adj5 (review$ or overview$)).tw. (182512)
244 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (11044)
245 ((studies or trial$) adj2 (review$ or overview$)).tw. (50319)
246 (integrat$ adj3 (research or review$ or literature)).tw. (12274)
247 (pool$ adj2 (analy$ or data)).tw. (39088)
248 (handsearch$ or (hand adj3 search$)).tw. (10367)
249 (manual$ adj3 search$).tw. (6726)
250 or/237-249 (2946278)
251 236 and 250 (880)
252 87 or 111 or 152 or 172 or 181 or 207 or 217 or 223 (9301)
253 limit 252 to yr="2000 -Current" (7335)
254 limit 253 to english language (6914)
255 (letter or editorial).pt. (1642662)
256 254 not 255 (6724)
257 (conference abstract or conference paper or conference proceeding or "conference review").pt. (3992679)
258 256 not 257 (5411)
259 exp Clinical Trial/ (1351675)
260 Randomization/ (80377)
261 Placebo/ (327770)
262 Double Blind Procedure/ (156158)
263 Single Blind Procedure/ (33348)
264 Crossover Procedure/ (57588)
265 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (1518430)
266 (random$ adj3 allocat$).tw. (39743)
267 placebo$.tw. (282204)
268 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (218646)
269 (crossover$ or (cross adj over$)).tw. (96932)
270 or/259-269 (2569830)
271 258 and 270 (392)
272 Clinical study/ (151360)
273 Case control study/ (134642)
274 Family study/ (25051)
275 Longitudinal study/ (119656)
276 Retrospective study/ (718231)

277 comparative study/ (784753)
278 Prospective study/ (489796)
279 Randomized controlled trials/ (154571)
280 278 not 279 (484845)
281 Cohort analysis/ (425623)
282 cohort analy$.tw. (10370)
283 (Cohort adj (study or studies)).tw. (240284)
284 (Case control$ adj (study or studies)).tw. (121202)
285 (follow up adj (study or studies)).tw. (58405)
286 (observational adj (study or studies)).tw. (135950)
287 (epidemiologic$ adj (study or studies)).tw. (97991)
288 (cross sectional adj (study or studies)).tw. (176084)
289 case series.tw. (86257)
290 prospective.tw. (752753)
291 retrospective.tw. (733504)
292 or/272-277,280-291 (3461297)
293 256 and 292 (604)
294 251 or 271 or 293 (1604)
295 256 not 294 (5199)

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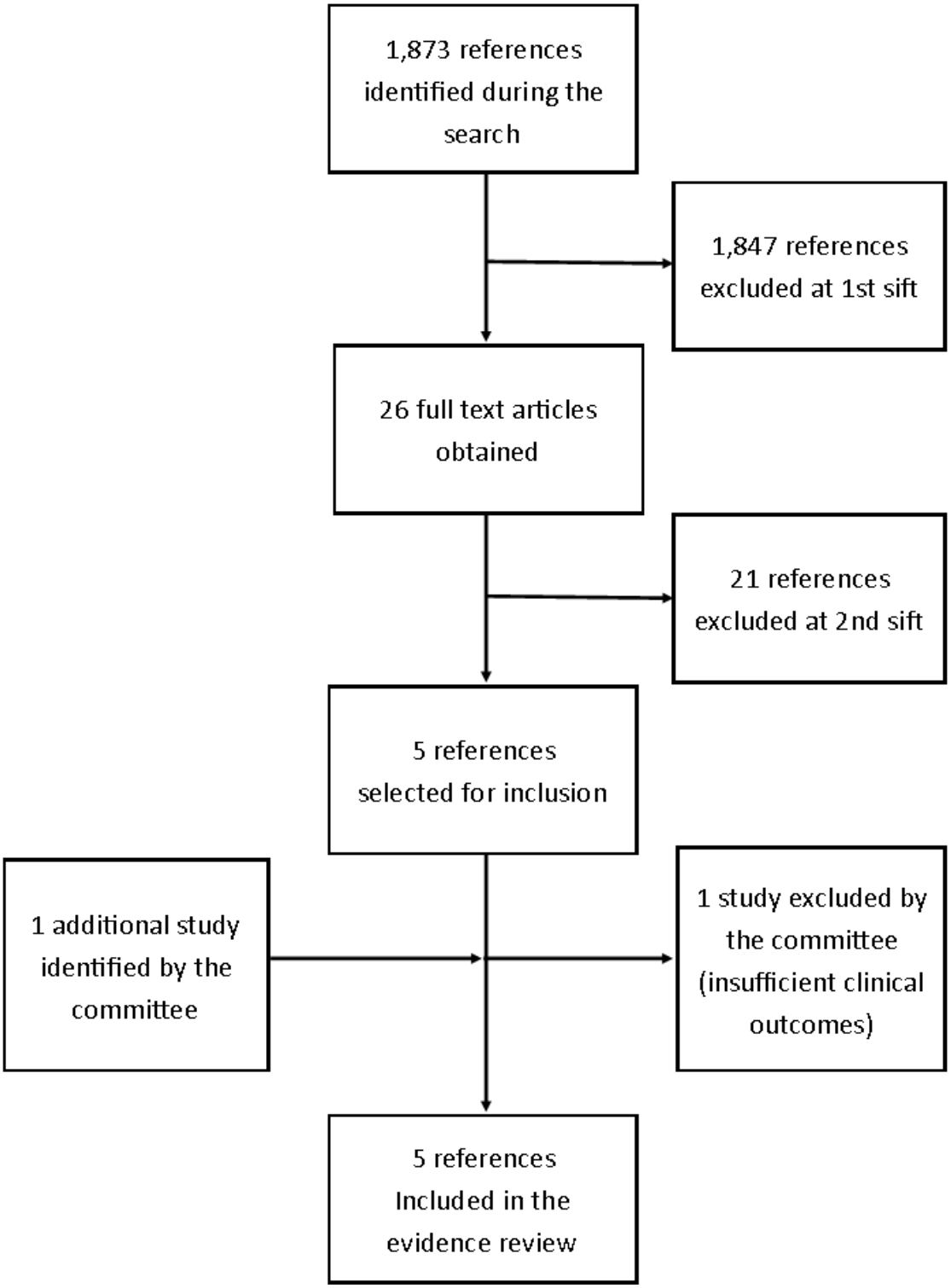
Appendix D: Study flow diagram



Appendix E: Included studies

Dyachenko P and Rozenman MZ (2006) Epidemiological and clinical manifestations of patients hospitalized with brown recluse spider bite. *Journal of the European Academy of Dermatology and Venereology.* 20(9) pages 1121 to 1125

Foex BA and Lee C (2006) Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. Oral antihistamines for insect bites. *Emergency Medical Journal*. 23. Pages 721 to 727

Friedland HD, O'Neal T, Biek D et al (2012) CANVAS 1 and 2: Analysis of Clinical Response at Day 3 in Two Phase 3 Trials of Ceftaroline Fosamil versus Vancomycin plus Aztreonam in Treatment of Acute Bacterial Skin and Skin Structure Infections. *Antimicrobial Agents and Chemotherapy*. 2012 May; 56(5): 2231–2236.

Karpinnen A, Brummer-Korvenkontio H, Petman L et al (2006) Levocetirizine for Treatment of Immediate and Delayed Mosquito Bite Reactions. *Acta Derm Venerol*. 86. Pages 329 to 331

Karpinnen A, Brummer-Korvenkontio H, Reunala T et al (2012) Rupatadine 10 mg in the treatment of immediate mosquito-bite allergy. *Journal of the European Academy of Dermatology and Venereology.* 26. Pages 919 to 922

Appendix F:Quality assessment of included studies

F.1 Antibiotics in adults with an infected arthropod bite

Table 3: Overall risk of bias/quality assessment – randomised controlled trials (Cochrane Risk of Bias tool)

Study reference	Friedland et al 2012
Domain 1: Risk of bias arising from the randomization process: Was the allocation sequence random? Was the allocation sequence concealed until participants were enrolled and assigned to interventions? Did baseline differences between intervention groups suggest a problem with the randomization process?	
Risk-of-bias judgement	**Low -** the trial is described as double blind; block randomisation using an interactive voice response system was used. Allocation concealment is not described; no baseline differences between groups were reported.
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention): Were participants / carers / people delivering the intervention aware of their assigned intervention during the trial? Were there deviations from the intended intervention that arose because of experimental context? If so, were the deviations balanced? If not, are they likely to have affected the outcome? Was the effect of assignment to the intervention analysed? If not, was there potential for a substantial impact on the result of the failure to do this?	
Risk-of-bias judgement	**Some concerns** – the trial is described as double blind except an unblinded pharmacist or unblinded study staff were used to adjust drug dose according to renal function. No method of allocation concealment is described. No deviations from intended intervention was reported; details regarding analysis used to estimate the effect of assignment to intervention appears to be a naïve per protocol.
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention): Were participants / carers / people delivering the intervention aware of their assigned intervention during the trial? If yes, were important co-interventions balanced across intervention groups? Could failures in implementing the intervention have affected the outcome? Did study participants adhere to the assigned intervention regimen? If not, was an appropriate analysis used to estimate the effect of adhering to the intervention?	
Risk-of-bias judgement	**Some concerns** – no method of blinding or allocation concealment is described except the trial is reported as double blind; 24 participants in the ceftaroline and 32 in the vancomycin/aztreonam arms were lost to follow-up, details of withdrawals and losses are reported in the study, although the largest group of withdraws are reported as simply lost to follow-up (33 people).
Domain 3: Missing outcome data: Were data for this outcome available for all or nearly all participants randomised? If not, is there evidence that the result was not biased by missing outcome data? If not, could missingness in the outcome depend on its true value? If so, do the proportions of missing outcome data differ between intervention groups? If so, is it likely that missingness in the outcome depended on its true value?	
Risk-of-bias judgement	**Low -** all participant data was available

Domain 4: Risk of bias in measurement of the outcome: Was the method of measuring the outcome inappropriate? Could it have been different between groups? If no to both, were the outcome assessors aware of the intervention received? If yes, could assessment of outcome have been influenced by knowledge of intervention? If so, is it likely?	
Risk-of-bias judgement	**Low** – Clinical response at day 3 was defined as meeting both of the following criteria: cessation of infection spread (no increase in baseline lesion width or length measurement) and absence of fever (temperature ≤37.6°C). Those not meeting criteria were considered non-responders. In addition, patients who were considered by the investigator as clinical failures on day 3 or who had missing or incomplete information on day 3 were also considered non-responders. Assessors were blinded.
Domain 5: Risk of bias in selection of the reported result: Was the trial analysed in accordance with pre-specified plan? Is the result likely to have been selected on the basis of results either from multiple outcome measurements or multiple analyses of data?	
Risk-of-bias judgement	**Low** – analysed in accordance with pre-specified plan, and not selected based on outcome measurements or multiple analyses of the data.
Overall risk-of-bias judgement	**Low**
Optional: What is the overall predicted direction of bias due to selection of the reported result?	**Unpredictable**

F.2 Oral antihistamines in people with an uninfected mosquito bite

Table 4: Overall risk of bias/quality assessment – systematic review (ROBIS systematic review checklist)

Study reference	Foex et al 2006
DOMAIN 1: IDENTIFYING CONCERNS WITH THE REVIEW PROCESS: *Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:*	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably Yes – no predefined eligibility criteria were stated; the objective was specified.
1.2 Were the eligibility criteria appropriate for the review question?	No Information - no predefined eligibility criteria were stated
1.3 Were eligibility criteria unambiguous?	No Information - no predefined eligibility criteria were stated
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	No Information - no predefined eligibility criteria were stated

1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	No Information - no predefined eligibility criteria were stated
DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES - Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably Not – the authors only searched Medline 1966–30.09.2005, CINAHL (R)-1982 to date 4th Oct 2005, and the Cochrane Library
2.2 Were methods additional to database searching used to identify relevant reports?	Probably Not – the authors do not report any searching additional to the database searches detailed above
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably Not – the authors did not search for all relevant antihistamine drugs and drug names (generic names only)
2.4 Were restrictions based on date, publication format, or language appropriate?	No Information – no details of any restrictions were reported
2.5 Were efforts made to minimise error in selection of studies?	No Information – no details about study selection was reported
DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL - Describe methods of study identification and selection (e.g. number of reviewers involved):	
3.1 Were efforts made to minimise error in data collection?	No Information – no details about data collection or data checking were reported, only that 1 author wrote the review and it was checked by 1 other reviewer
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes – the study accurately reported the populations, interventions and comparators
3.3 Were all relevant study results collected for use in the synthesis?	Yes – the included studies only generally reported 2 clinical outcomes (pruritus and cutaneous reactions)
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	No – the authors reported ‘study weaknesses’ but no formal assessment of study quality
3.5 Were efforts made to minimise error in risk of bias assessment?	No Information – no details of risk of bias assessment reported
DOMAIN 4: SYNTHESIS AND FINDINGS Describe synthesis methods:	
4.1 Did the synthesis include all studies that it should?	Probably Yes – the NICE search uncovered no additional RCTs to those identified by the authors
4.2 Were all pre-defined analyses reported or departures explained?	No Information – it is unclear if the authors intended to undertake further analyses of the included studies (the results are reported narratively - not pooled)

4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	No meta-analyses were performed - all data was reported narratively.	
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	No detail was provided on statistical heterogeneity.	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	No additional analyses were performed – all data were reported narratively.	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	No the studies were not explicitly evaluated for quality or risk of bias. Bias was not explicitly addressed in the synthesis.	
PHASE 3: JUDGING RISK OF BIAS	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria	Unclear	No predefined study eligibility criteria reported
2. Concerns regarding methods used to identify and/or select studies	High	Inadequate search strategy (places searched and search terms and methods)
3. Concerns regarding methods used to collect data and appraise studies	High	No predefined data extraction or analysis plan
4. Concerns regarding the synthesis and findings	High	Study findings were reported narratively (no synthesis). Individual studies were not formally assessed for risk of bias, nor was potential bias accounted for in the synthesis. There was no discussion or assessment of heterogeneity in the analysis.
RISK OF BIAS IN THE REVIEW: Describe whether conclusions were supported by the evidence:		
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Probably Yes – the study used a clinical scenario and answered with an appropriate clinical interpretation of the study findings	
B. Was the relevance of identified studies to the review's research question appropriately considered?	Probably Yes – in the search outcome section of the review the authors considered whether the RCTs addressed the review question	
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes – the review does not present the p values from the included RCTs	
Risk of bias in the review RISK: Rationale for risk:	High – due to a lack of predefined eligibility criteria, predefined analysis plan and an absence of risk of bias assessment of the included studies.	

Table 5: Overall risk of bias/quality assessment – randomised controlled trials (Cochrane Risk of Bias tool)

Study reference	Karpinnen et al 2006	Karpinnen et al 2012
Domain 1: Risk of bias arising from the randomization process:		

Was the allocation sequence random? Was the allocation sequence concealed until participants were enrolled and assigned to interventions? Did baseline differences between intervention groups suggest a problem with the randomization process?		
Risk-of-bias judgement	**High -** the trial is described as double blind; no method of blinding or allocation concealment is described; no baseline differences between groups were obtained or reported.	**High -** the trial is described as double blind; no method of blinding or allocation concealment is described; no baseline differences between groups were obtained or reported.
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention): Were participants / carers / people delivering the intervention aware of their assigned intervention during the trial? Were there deviations from the intended intervention that arose because of experimental context? If so, were the deviations balanced? If not, are they likely to have affected the outcome? Was the effect of assignment to the intervention analysed? If not, was there potential for a substantial impact on the result of the failure to do this?		
Risk-of-bias judgement	**Some concerns** – the trial is described as double blind but is also a crossover design, no method of blinding or allocation concealment is described, participants were probably aware that they would receive an active treatment and placebo at different times. No deviations from intended intervention was reported; details regarding analysis used to estimate the effect of assignment to intervention appears to be a naïve per protocol.	**Some concerns** – the trial is described as double blind but is also a crossover design, no method of blinding or allocation concealment is described, participants were probably aware that they would receive an active treatment and placebo at different times. No deviations from intended intervention was reported; details regarding analysis used to estimate the effect of assignment to intervention appears to be a naïve per protocol.
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention): Were participants / carers / people delivering the intervention aware of their assigned intervention during the trial? If yes, were important co-interventions balanced across intervention groups? Could failures in implementing the intervention have affected the outcome? Did study participants adhere to the assigned intervention regimen? If not, was an appropriate analysis used to estimate the effect of adhering to the intervention?		
Risk-of-bias judgement	**Some concerns** – no method of blinding or allocation concealment is described; 2 participants lost to follow-up, 1 participant withdrew (due to a respiratory infection) and 1 further participant was excluded from the analysis due to very small skin reaction (whealing) to bites while on placebo treatment (population was mosquito bite *sensitive* people).	**Some concerns** – no method of blinding or allocation concealment is described; 4 participants lost to follow-up (although all participants were included for safety outcome), 1 participant did not have all efficacy evaluations undertaken and was excluded, 2 participants were excluded from the analysis due to small bite reaction (whealing) smaller than 25 mm^2. 1 participant bite size at 15 minutes was 50% smaller than baseline and so was excluded.
Domain 3: Missing outcome data: Were data for this outcome available for all or nearly all participants randomised? If not, is there evidence that the result was not biased by missing outcome data? If not, could missingness in the outcome depend on its true value? If so, do the proportions of missing outcome data differ between intervention groups? If so, is it likely that missingness in the outcome depended on its true value?		
Risk-of-bias judgement	**Low -** all participant data was available	**Low -** all participant data was available
Domain 4: Risk of bias in measurement of the outcome:		

Was the method of measuring the outcome inappropriate? Could it have been different between groups? If no to both, were the outcome assessors aware of the intervention received? If yes, could assessment of outcome have been influenced by knowledge of intervention? If so, is it likely?		
Risk-of-bias judgement	**Low** – bite skin reaction was measured by investigators using 2 perpendicular diameters in mm. Pruritus was self-assessed using a 100 mm visual analogue scale; both outcomes appear to be measured appropriately; it is unclear if the outcome assessors were aware of the intervention received. As the study was short term and crossover design it is unlikely that assessment outcome would have been influenced by knowledge of the intervention.	**Some concerns** – bite skin reaction was measured in 2 perpendicular diameters expressed as mm^2; no details were provided on who undertook the measurement. Pruritus was self-assessed using a 100 mm visual analogue scale. It is unclear if the outcome assessors were aware of the intervention received. As the study was short term and crossover design it is unlikely that assessment outcome would have been influenced by knowledge of the intervention.
Domain 5: Risk of bias in selection of the reported result: Was the trial analysed in accordance with pre-specified plan? Is the result likely to have been selected on the basis of results either from multiple outcome measurements or multiple analyses of data?		
Risk-of-bias judgement	**High** – analysed in accordance with pre-specified plan, and not selected based on outcome measurements or multiple analyses of the data. Non-parametric tests were used which are distribution free and inappropriate when trying to determine an estimate of effect and they lack power. The author did not transform the data prior to analysing the results.	**High** – analysed in accordance with pre-specified plan, and not selected based on outcome measurements or multiple analyses of the data. Non-parametric tests were used which are distribution free and inappropriate when trying to determine an estimate of effect and they lack power. The author did not transform the data prior to analysing the results.
Overall risk-of-bias judgement	**Some concerns**	**Some concerns**
Optional: What is the overall predicted direction of bias due to selection of the reported result?	**Unpredictable**	**Unpredictable**

F.3 Treatments for people with an uninfected brown recluse spider bite

Table 6: Overall risk of bias/quality assessment – observational studies (Case Series Studies)

Study reference	Dyachenko and Rozenman 2006
Was the hypothesis/aim/objective of the study clearly stated?	Yes – the aim of the study was to examine documented loxosceles species spider envenomation and the natural history of affected people

Was the study conducted prospectively?	No – the study was conducted retrospectively (cases from between 1997 and 2004)
Were the cases collected in more than one centre?	No – this was a single centre study (Ha'emek Medical Centre, northern Israel)
Were patients recruited consecutively?	Unclear – only cases in which the clinical manifestation of loxosceles envenomation was present were included.
Were the characteristics of the patients included in the study described?	Yes – age, gender, comorbid disease, time of year of bite injury were all reported.
Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes - only cases in which the clinical manifestation of loxosceles envenomation was present were included.
Did patients enter the study at a similar point in the disease?	Unclear – the authors report that the interval between the time of the bite and presentation to hospital was >24 hours in 65% cases (no further details reported).
Was the intervention of interest clearly described?	Yes – although multiple interventions are described, and these are not clearly linked to clinical outcome.
Were additional interventions (co-interventions) clearly described?	Yes – although multiple interventions are described, and these are not clearly linked to clinical outcome.
Were relevant outcome measures established a priori?	Unclear – as this was a retrospective study with natural history as its key outcome rather than clinical outcome.
Were outcome assessors blinded to the intervention that patients received?	Not applicable.
Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes – tissue necrosis, time to healing and length of hospital stay were measured.
Were the relevant outcome measures made before and after the intervention?	Not applicable.
Were the statistical tests used to assess the relevant outcomes appropriate?	Yes – Parametric data was analysed using Student's *t*-test, one-way ANOVA and Pearson's correlation. Chi-square test was used to compare proportions.
Was follow-up long enough for important events and outcomes to occur?	No – hospital data alone was used and there was no longer term primary care follow-up described.
Were losses to follow-up reported?	Not applicable.
Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Not applicable.
Were the adverse events reported?	No – no treatment related adverse events were reported.
Were the conclusions of the study supported by results?	Yes – the authors reported the natural history of the bite and cautiously advised systemic treatment might be of benefit.

Were both competing interests and sources of support for the study reported?	No – no conflicts of interest were declared.

Appendix G: GRADE profiles

G.1 Antibiotics in adults with an infected arthropod bite

Table 7: GRADE profile – IV ceftaroline compared with IV vancomycin and IV aztreonam for arthropod bites in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftaroline (IV)	Vancomycin and aztreonam (IV)	Relative (95% CI)	Absolute		
Clinical response at day 3 (follow-up 3 days; assessed with: cessation of infection spread and absence of fever (<37.6C)[1])												
1[2]	randomised trials[3]	no serious risk of bias	no serious inconsistency	serious[4]	serious[5]	none[6]	8/9 (88.9%)[6]	6/10 (60%)[7]	RR 1.48 (0.85 to 2.58)	288 more per 1000 (from 90 fewer to 948 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: IV, Intravenous; 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial.												

[1] Although the phase 3 CANVAS trials used a traditional study design with a clinical cure evaluation at TOC, relevant data were collected during the study to allow analysis of clinical response rates (i.e., cessation of lesion spread and absence of fever) at day 3. A retrospective analysis of the individual and combined CANVAS trials was performed using a clinical response endpoint at day 3 in a subgroup of patients who met the FDA definition of ABSSSI. This is the first analysis conducted in this indication for a new drug application approval that is based on FDA guidance.
[2] Friedland et al 2012.
[3] Double-blind, non-inferiority RCT.
[4] The original trial included people with human and animal bites, this secondary analysis reports n=19 people with extensive cellulitis due to arthropod bite as a subgroup of the n=1,378 adults originally enrolled in the CANVAS 1 and 2 trials. It is unclear what arthropods were involved.
[5] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with intravenous ceftaroline.
[6] The small post hoc subgroup will have violated the original non inferiority margin of the original trials leading to possible under or over estimation of effect
[7] Intervention was IV ceftaroline 600 mg twice daily for 5 to 14 days.
[8] Control was IV vancomycin 1 g and IV aztreonam 1 g twice daily for 5 to 14 days.

G.2 Oral antihistamines for adults with an uninfected mosquito bite

Table 8: GRADE profile – cetirizine compared with placebo for mosquito bites in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cetirizine	Placebo	Relative (95% CI)	Absolute		
Bite lesion size/erythema (follow-up 10 minutes; measured with cetirizine versus placebo; better indicated by lower values)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	very serious[4]	none	9[5]	9[6]	Mean surface area cetirizine 39.7 mm^2 (±14.1 mm^2 SEM) Mean surface area placebo 54.3 mm^2 (±12.1 mm^2 SEM)	MD −14.60 (95% CI −51.02 to 21.82)[7]	⊕OOO VERY LOW	CRITICAL
Bite lesion size[8] (follow-up 15 minutes; measured with cetirizine versus placebo; better indicated by lower values)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[9]	serious[10]	none	27[11]	27[12]	Median bite lesion size (cetirizine) 25 mm^2 (IQR 12 and 25 mm^2) Median bite lesion size (placebo) 28 mm^2 (IQR 16 and 63 mm^2) Cetirizine significantly reduced bite lesion size compared with placebo (p=0.003)		⊕⊕OO LOW	CRITICAL
Bite lesion size[8] (follow-up 15 minutes: measured with cetirizine versus placebo; better indicated by lower values)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	serious[13]	none	18[14]	18[15]	Mean bite lesion size (cetirizine) 5.9 ±5.9 mm (SD) Mean bite lesion size (placebo) 10.1 ±10.4 mm (SD)	MD −4.20 (95% CI −9.72 to 1.32)[7, 16]	⊕⊕OO LOW	CRITICAL
Bite lesion size[17] before and after treatment (follow-up 15 minutes; measured with cetirizine versus placebo; better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	not applicable	serious[3]	serious[10]	none	11[18]	12[19]	Mean bite lesion size significantly smaller with cetirizine (p<0.01) Mean bite lesion size with placebo (NS)		⊕⊕OO LOW	CRITICAL
Bite lesion size[17] before and after treatment (follow-up 60 minutes; measured with cetirizine versus placebo; better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	not applicable	serious[3]	serious[10]	none	11[18]	12[19]	Mean bite lesion size with cetirizine (NS) Mean bite lesion size with placebo (NS)		⊕⊕OO LOW	CRITICAL
Bite lesion size[8] (follow-up 60 minutes; measured with cetirizine versus placebo; better indicated by lower values)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	serious[20]	none	18[14]	18[15]	Mean bite lesion size (cetirizine) 8.3±6.7 mm (SD) Mean bite lesion size (placebo) 11.7±10.5 mm (SD)	MD −3.40 (95% CI −9.15 to 2.35)[7,16]	⊕⊕OO LOW	CRITICAL
Bite lesion size[8] (follow-up 12 hours; measured with cetirizine versus placebo; better indicated by lower values)												
1[1]	randomised trials[2]	no serious	not applicable	serious[3]	serious[21]	none	18[14]	18[15]	Mean bite lesion size (cetirizine) 8.5±12.7 mm (SD)	MD −5.20 (95% CI −16.07 to 5.67)[7, 22]	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cetirizine	Placebo	Relative (95% CI)	Absolute		
		risk of bias							Mean bite lesion size (placebo) 13.7±19.8 mm (SD)			
Mean bite lesion size[8] (follow-up 24 hours; measured with cetirizine versus placebo; better indicated by lower values)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	serious[23]	none	18[14]	18[15]	Mean bite lesion size (cetirizine) 7.4±16.1 mm (SD) Mean bite lesion size (placebo) 12.6±21.9 mm (SD)	MD −5.20 (95% CI −17.76 to 7.36)[7, 24]	⊕⊕OO LOW	CRITICAL
Mean bite lesion surface area-delayed recurrence (follow-up 12 to 24 hours; measured with cetirizine versus placebo; better indicated by lower values)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	serious[10]	none	9[5]	9[6]	1 RCT reported NS difference between cetirizine and placebo groups (trend; p=0.08). Authors reported that delayed reactions usually lasted 1 to 2 weeks		⊕⊕OO LOW	CRITICAL
Pruritus[25] (follow-up 15 minutes; measured with cetirizine versus placebo; better indicated by lower values)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[9]	serious[10]	none	27[11]	27[12]	Median pruritus (VAS) cetirizine 0 (IQR 0 and 30) Median pruritus (VAS) placebo 50 (IQR 10 and 70) Cetirizine significantly reduced pruritus compared with placebo (p<0.001)		⊕⊕OO LOW	CRITICAL
Pruritus[25] before and after treatment (follow-up 15 minutes; measured with cetirizine versus placebo; better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	not applicable	serious[3]	serious[10]	none	11[18]	12[19]	Mean pruritus score with cetirizine (p<0.01) Mean pruritus score with placebo (NS)		⊕⊕OO LOW	CRITICAL
Pruritus[26] (follow-up at 15 minutes; measured with cetirizine versus placebo: better indicated by lower values)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	serious[27]	none	18[14]	18[15]	Mean pruritus score with cetirizine 11.2 ± 13.2 (SD) Mean pruritus score with placebo 36.0 ± 25.2 (SD)	MD −24.80 (95% CI −37.94 to −11.66)[7]	⊕⊕OO LOW	CRITICAL
Pruritus[26] (follow-up at 60 minutes; measured with cetirizine versus placebo: better indicated by lower values)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	serious[28]	none	18[14]	18[15]	Mean pruritus score with cetirizine 9.8 ± 12.7 (SD) Mean pruritus score with placebo 27.7 ± 25.1 (SD)	MD −17.90 (95% CI −30.90 to −4.90)[7]	⊕⊕OO LOW	CRITICAL
Pruritus[25] before and after treatment (follow-up 60 minutes; measured with cetirizine versus placebo; Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	not applicable	serious[3]	serious[10]	none	11[18]	12[19]	Mean pruritus score with cetirizine (NS) Mean pruritus score with placebo (NS)		⊕⊕OO LOW	CRITICAL
Pruritus[26] before and after treatment (follow-up 12 hours; measured with cetirizine versus placebo; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cetirizine	Placebo	Relative (95% CI)	Absolute		
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	serious[29]	none	18[14]	18[15]	Mean pruritus score with cetirizine 6.2 ± 13.3 Mean pruritus score with placebo 18.7 ± 20.9	MD −12.50 (95% CI −23.94 to −1.06)[7, 30]	⊕⊕OO LOW	CRITICAL
Pruritus[26] before and after treatment (follow-up 24 hours; measured with cetirizine versus placebo; Better indicated by lower values)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	serious[31]	none	18[14]	18[15]	Mean pruritus score with cetirizine 6.6 ± 14.8 Mean pruritus score with placebo 18.9 ± 25.5	MD −12.30 (95% CI −25.92 to 1.32)[7, 32]	⊕⊕OO LOW	CRITICAL
Pruritus[33] (follow-up at 10, 30 and 90 minutes, then daily up from days 2 to 10; measured with cetirizine versus placebo; Better indicated by lower values)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	serious[10]	none	9[5]	9[6]	The authors report NS difference in pruritus at 10, 30 and 90 minutes and days 2, 5 and from days 7 to 10. There were significant differences (favours cetirizine at days 3 (p<0.01), 4 (p<0.05) and 6 (p<0.05).		⊕⊕OO LOW	CRITICAL
Adverse effects (mild to severe sedation) (follow-up time period not reported; assessed with cetirizine versus placebo)												
3[1]	randomised trials[2]	no serious risk of bias	no inconsistency	serious[3]	very serious[34]	none	15/65 (23%)	7/66 (10.6%)	RR 2.17 (0.95 to 4.94)[7]	124 more per 1000 (from 5 fewer to 418 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (headache, emesis or arthralgia[35]) (follow-up time period not reported; assessed with cetirizine versus placebo)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	very serious[36]	none	3/27[14] (11.1%)	4/27[15] (14.8%)	RR 0.75 (0.19 to 3.04)[7]	37 fewer per 1000 (from 120 fewer to 302 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (follow-up time period not reported; assessed with cetirizine versus placebo)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	serious[10]	none	9[5]	9[6]	Rescue treatment (not defined) was used by 4 participants in the placebo group. Transient drowsiness (1 day) was reported in the cetirizine group (unclear how many participants affected). 1 participant in the placebo group reported drowsiness and dry mouth (unclear duration).		⊕⊕OO LOW	CRITICAL
Patient preference for treatment (follow-up time period not reported; assessed with cetirizine versus placebo)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	serious[10]	none	9[5]	9[6]	In 1 RCT (n=9) 7 individuals preferred cetirizine, 1 individual preferred placebo and 1 individual had no preference.		⊕⊕OO LOW	CRITICAL

Abbreviations: 95% CI, 95% Confidence interval; IQR, Interquartile range; VAS, Visual analogue scale; p, P value; RR, Relative risk; RCT, Randomised controlled trial; NS, Not statistically significant.

[1] Foex et al 2006 systematic review (additional information on effects size and adverse effects taken from included RCT papers)
[2] Double-blind, cross-over RCT
[3] Downgraded 1 level – healthy adult volunteers with bite exposure but without infection

[4] Downgraded 2 levels - at a default minimal important difference of 0.5 standard deviation of the placebo arm (18.15 mm^2) relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with cetirizine, and no meaningful difference or appreciable harm with placebo (NS result for authors also p=0.32)
[5] Cetirizine 10 mg two times a day for 4 days (followed by 10 days washout)
[6] Placebo tablet two times a day (followed by 10 days washout)
[7] NICE analysis
[8] Bite lesion size measured as 2 perpendicular diameters
[9] Downgraded 1 level - population were people who were mosquito bite sensitive, with bite exposure but without infection
[10] Downgraded 1 level – data not adequately presented/not re-calculable
[11] Cetirizine 10 mg taken daily at 8 am for 4 days (followed by 3 days washout)
[12] Placebo taken daily at 8 am for 4 days (followed by 3 days washout)
[13] Downgraded 1 level – at a default minimal important difference of 0.5 standard deviation of the placebo arm (5.2 mm) relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with cetirizine
[14] Cetirizine 10 mg taken daily at 8 am for 7 days (no washout period mentioned)
[15] Placebo taken daily at 8 am for 7 days (no washout period mentioned)
[16] Authors report p<0.05 using ANOVA (analysis of variance)
[17] Bite diameter in mm
[18] 5-day baseline exposure, followed by cetirizine 10 mg once daily for 5 days
[19] 5-day baseline exposure, followed by placebo once daily for 5 days
[20] Downgraded 1 level – at a default minimal important difference of 0.5 standard deviation of the placebo arm (5.25 mm) relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with cetirizine
[21] Downgraded 1 level – at a default minimal important difference of 0.5 standard deviation of the placebo arm (9.9 mm) relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with cetirizine
[22] Authors report p<0.05 using ANOVA (analysis of variance), a second RCT found no significant difference in bite lesions with cetirizine compared with placebo at 12 hours (n=10; p=0.49)
[23] Downgraded 1 level – at a default minimal important difference of 0.5 standard deviation of the placebo arm (10.95 mm) relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with cetirizine
[24] Authors report p<0.01 using ANOVA (analysis of variance), a second RCT also found no significant difference in bite lesions with cetirizine compared with placebo at 24 hours (n=12; p=0.46)
[25] Pruritus was evaluated using a 100-mm visual analogue scale (VAS) ranging from 0 (no pruritus) to 100 (very intense pruritus)
[26] Pruritus measured using an 8 cm visual analogue scale ranging from 0 (no pruritus) to 100 (very intense pruritus)
[27] Downgraded 1 level – at a default minimal important difference of 0.5 standard deviation of the placebo arm (12.6) relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with cetirizine
[28] Downgraded 1 level – at a default minimal important difference of 0.5 standard deviation of the placebo arm (12.55) relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with cetirizine
[29] Downgraded 1 level – at a default minimal important difference of 0.5 standard deviation of the placebo arm (10.45) relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with cetirizine
[30] Authors report p<0.01 using ANOVA (analysis of variance), a second RCT found no significant difference in pruritis at 12 hours (n=10; p=0.46)
[31] Downgraded 1 level – at a default minimal important difference of 0.5 standard deviation of the placebo arm (12.75) relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with cetirizine
[32] Authors report p<0.01 using ANOVA (analysis of variance), a second RCT found no significant difference in pruritis at 24 hours (n=9; p=0.77)
[33] Pruritus evaluated using a 0 to 10 visual analogue scale (0 being total lack of symptoms and 10 the worst conceivable condition)
[34] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with cetirizine, and no meaningful difference or appreciable benefit with placebo, also very wide 95% confidence intervals (0.95 to 4.94)
[35] The authors reported that they did not feel these adverse effects were drug related and suggested they were associated with acute infection (not further defined), menses or dental treatment
[36] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with cetirizine, and no meaningful difference or appreciable harm with placebo, also very wide 95% confidence intervals (0.19 to 3.04)

Table 9: GRADE profile – levocetirizine compared with placebo for mosquito bites in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antihistamine	Placebo	Relative (95% CI)	Absolute		
Wheal size (follow-up 15 minutes; measured with: levocetirizine versus placebo; Better indicated by lower values)												
1[1]	randomised trials[2]	serious[15]	not applicable	serious[3]	serious[4]	none	28[5]	28[6]	Median wheal size (levocetirizine) 27 mm^2 (IQR 20 and 40 mm^2); Median wheal size (placebo) 68 mm^2 (IQR 34 and 104 mm^2); 60% reduction in median wheal size with levocetirizine at 15 minutes (p<0.001)[7, 8]		VERY LOW	CRITICAL
Pruritus (follow-up 15 minutes; measured with: levocetirizine versus placebo[9]; Better indicated by lower values)												
1[1]	randomised trials[2]	serious[15]	not applicable	serious[3]	serious[4]	none	28[5]	28[6]	Median VAS (levocetirizine) 3 (IQR 1 and 5); Median VAS (placebo) 8 (IQR 7 and 9); 62% reduction in VAS for pruritus with levocetirizine at 15 minutes (p<0.001)[7, 10]		VERY LOW	CRITICAL
Delayed bite lesions[11] size (follow-up 24 hours; measured with: levocetirizine versus placebo; Better indicated by lower values)												
1[1]	randomised trials[2]	serious[15]	not applicable	serious[3]	serious[4]	none	8[5]	8[6]	Median bite lesion size (levocetirizine) 71 mm^2 (range 0 to 460 mm^2); Median bite lesion size (placebo) 240 mm^2 (range 28 to 690 mm^2); 71% reduction in median bite lesion with levocetirizine at 24 hours (p=0.008)[7]		VERY LOW	CRITICAL
Delayed bite lesions[11] pruritus (follow-up 24 hours; measured with: levocetirizine versus placebo[7]; Better indicated by lower values)												
1[1]	randomised trials[2]	serious[15]	not applicable	serious[3]	serious[4]	none	8[5]	8[6]	Mean VAS (levocetirizine) 2.0 (range 0 to 6); Mean VAS (placebo) 4.75 (range 2 to 8); 56% reduction in VAS for pruritus with levocetirizine at 24 hours (p=0.016)[7]		VERY LOW	CRITICAL
Adverse effects (follow-up time period not reported; assessed with mild to moderate somnolence[12])												
1[1]	randomised trials	serious[15]	not applicable	serious[3]	very serious[13]	none	5/28 (17.9%)[5]	2/28 (7.1%)[6]	RR 2.50 (0.53 to 11.82)[14]	107 more per 1000 (from 34 fewer to 773 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; IQR, Interquartile range; p, P value; RR, Relative risk; VAS, Visual analogue scale.												

[1] Karpinnen et al 2006
[2] Double-blind, cross-over trial.
[3] Downgraded 1 level - population were adults who were mosquito bite sensitive (at least 5 mm diameter wheal from mosquito bite), with bite exposure (bite exposure was performed with *A. aegypti* laboratory mosquitoes in both drug periods between 12.00 a.m. and 15.00 a.m. on day 3. Two mosquitoes in a cage were allowed to feed on the forearm) but without infection
[4] Downgraded 1 level - not re-calculable, medians and IQR or means and range only
[5] Levocetirizine 5 mg taken daily at 08.00 a.m. for 4 days followed by 3 days without any drugs (washout period)
[6] Placebo tablet taken daily at 08.00 a.m. for 4 days followed by 3 days without any drugs (washout period)
[7] P values calculated using Wilcoxon's signed rank test with Hommel's adjusted p-value
[8] Levocetirizine effect increased in a linear fashion, most significant in subjects with large wheals (*r*-0.91; 95% CI -0.96 to -0.82), no correlation methods provided
[9] Pruritus was evaluated using a 100-mm visual analogue scale (VAS) ranging from 0 (no pruritus) to 100 (very intense pruritus)
[10] Authors state there was no correlation with severity of pruritus (data not provided)
[11] Lesion size >5 mm diameter lesion at 24 hours

[12] NICE analysis - 28 people assessed in cross-over 5 subjects on levocetirizine and 2 on placebo experienced mild to moderate somnolence, no details of how outcome assessed
[13] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with levocetirizine, and no meaningful difference or appreciable benefit with placebo
[14] NICE analysis
[15] Downgraded 1 level- serious risk of bias because non-parametric statistics used which lack power and are inappropriate.

Table 10: GRADE profile – loratadine compared with placebo for mosquito bites in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Loratadine	Placebo	Relative (95% CI)	Absolute		
Bite lesion size (follow-up 15 minutes; measured with: loratadine versus placebo; Better indicated by lower values)												
1[1]	randomised trials	serious[9]	not applicable	serious[2]	serious[3]	none	27[4]	27[5]	Median bite lesion size (loratadine) 25 mm^2 (IQR 16 and 48 mm^2) Median bite lesion size (placebo) 28 mm^2 (IQR 16 and 63 mm^2) Loratadine not significantly different to placebo (p=0.09)		⊕OOO VERY LOW	CRITICAL
Pruritus[6] (follow-up 15 minutes; measured with: loratadine versus placebo; Better indicated by lower values)												
1[1]	randomised trials	serious[9]	not applicable	serious[2]	serious[3]	none	27[4]	27[5]	Median pruritus (VAS) loratadine 30 (IQR 10 and 60) Median pruritus (VAS) placebo 50 (IQR 10 and 70) Loratadine not significantly different to placebo (p=0.067)		⊕OOO VERY LOW	CRITICAL
Adverse effects (mild to severe sedation) (follow-up unclear; assessed with loratadine versus placebo)												
1[1]	randomised trials	no serious risk of bias	not applicable	serious[2]	very serious[7]	none	5/27 (18.5%)[4]	4/27 (14.8%)[5]	RR 1.25 (0.38 to 4.16)[8]	37 more per 1000 (from 92 fewer to 468 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; IQR, Interquartile range; VAS, Visual analogue scale; p, P value; RR, Relative risk.												

[1] Karpinnen et al 2002
[2] Downgraded 1 level - population were people who were mosquito bite sensitive, with bite exposure but without infection
[3] Downgraded 1 level - not re-calculable, unclear if point estimates are means or medians and if the figures in brackets are ranges, interquartile ranges or 95% confidence intervals
[4] Loratadine 10 mg taken daily at 08:00 am for 4 days (followed by 3 washout days)
[5] Placebo tablet taken at 08:00 am for 4 days (followed by 3 washout days)
[6] Pruritus was evaluated using a 100-mm visual analogue scale (VAS) ranging from 0 (no pruritus) to 100 (very intense pruritus)
[7] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with loratadine, and no meaningful difference or appreciable benefit with placebo, also wide confidence intervals (0.38 to 4.16)
[8] NICE analysis
[9] Downgraded 1 level- serious risk of bias because non-parametric statistics used which lack power and are inappropriate.

Table 11: GRADE profile – rupatadine compared with placebo for mosquito bites in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rupatadine	Placebo	Relative (95% CI)	Absolute		
Wheal size (follow-up 15 minutes; measured with: rupatadine versus placebo; Better indicated by lower values)												
1[1]	randomised trials[2]	serious[12]	not applicable	serious[3]	serious[4]	none	26[5]	26[6]	Median wheal size (rupatadine) 55 mm^2; Median wheal size (placebo) 106 mm^2; 48% reduction in median wheal size with rupatadine (p<0.001)[7]		⊕OOO VERY LOW	CRITICAL
Pruritus (follow-up 15 minutes; measured with: rupatadine versus placebo[8]; Better indicated by lower values)												
1[1]	randomised trials[2]	serious[12]	not applicable	serious[3]	serious[4]	none	26[5]	26[6]	Median VAS (rupatadine) 47.5 mm^2; Median VAS (placebo) 60 mm^2; 21% reduction in median VAS for pruritus with rupatadine (p<0.05)[7]		⊕OOO VERY LOW	CRITICAL
Delayed bite lesions size (follow-up 24 hours; measured with: rupatadine versus placebo; Better indicated by lower values)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	serious[4]	none	26[5]	26[6]	Mean bite lesion size (rupatadine) 10.5 mm^2; Mean bite lesion size (placebo) 23 mm^2; 54% reduction in mean bite lesion size with rupatadine (*NS*)		⊕⊕OO LOW	CRITICAL
Delayed bite lesion size in adults reactive at 24 hours (follow-up 24 hours; measured with: rupatadine versus placebo; Better indicated by lower values)												
1[1]	randomised trials[2]	serious[12]	not applicable	serious[3]	serious[4]	none	20[5]	20[6]	Bite lesion size (rupatadine) 13.5 mm^2; Bite lesion size (placebo) 33 mm^2; 60% reduction in bite lesion size with rupatadine (p=0.07)[9]		⊕OOO VERY LOW	CRITICAL
Delayed bite lesions pruritus in adults reactive at 24 hours[8] (follow-up 24 hours; measured with: rupatadine versus placebo[7]; Better indicated by lower values)												
1[1]	randomised trials[2]	serious[12]	not applicable	serious[3]	serious[4]	none	10[5]	10[6]	23% reduction in VAS for pruritus[9] with rupatadine (*NS*) further data not reported		⊕OOO VERY LOW	CRITICAL
Adverse effects (follow-up time period not reported; assessed with sedation)												
1[1]	randomised trials	no serious risk of bias	not applicable	serious[3]	very serious[10]	none	8/26 (30.8%)[5]	1/26 (3.8%)[6]	RR 8.00 (1.08 to 59.50)[11]	269 more per 1000 (from 3 more to 1000 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: 95% CI, 95% Confidence interval; p, P value; VAS, Visual analogue scale; NS, Not statistically significant result (P value not reported); RR, Relative risk.

[1] Karpinnen et al 2012
[2] Double-blind, cross over RCT
[3] Downgraded 1 level - population were people who were mosquito bite sensitive, with bite exposure but without infection
[4] Downgraded 1 level - not re-calculable, only mean or median data reported
[5] Rupatadine 10 mg taken at 08:00 am for 4 days (5 day washout period), then alternative (placebo) given for 4 days
[6] Placebo tablet taken at 08:00 am for 4 days (5 day washout period), then alternative (rupatadine) given for 4 days
[7] P values calculated using Wilcoxon's signed rank test with Hummel's adjusted p-value
[8] Pruritus was evaluated using a 100-mm visual analogue scale (VAS) ranging from 0 (no pruritus) to 100 (very intense pruritus)
[9] Unclear whether the bite lesion size measurement is mean or median
[10] Downgraded 2 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with rupatadine, also very wide 95% confidence interval (1.08 to 59.50)

[11] NICE analysis - the authors report there was no significant difference in adverse events between the intervention and the comparator (8 cases in rupatadine and 4 cases in placebo). Eight people reported sedation in 9 cases (8 cases in rupatadine and 1 case in placebo)
[12] Downgraded 1 level- serious risk of bias because non-parametric statistics used which lack power and are inappropriate.

G.3 Oral antihistamines for children with an uninfected mosquito bite

Table 12: GRADE profile – loratadine compared with placebo for mosquito bites in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Loratadine	Placebo	Relative (95% CI)	Absolute		
Bite lesion size (follow-up 15 minutes; measured with: loratadine versus placebo; Better indicated by lower values)												
1[1]	randomised trials[2]	serious [11]	not applicable	serious[3]	serious[4]	none	25[5]	25[6]	Median bite lesion size (loratadine) 35 mm^2 (range 6 to 120 mm^2); Median bite lesion size (placebo) 64 mm^2 (range 9 to 400 mm^2); 45% reduction in bite lesion size with loratadine (p<0.001)[7]		⊕OOO VERY LOW	CRITICAL
Bite lesion size (follow-up 2 hours; measured with: loratadine versus placebo; Better indicated by lower values)												
1[1]	randomised trials[2]	serious [11]	not applicable	serious[3]	serious[4]	none	25[5]	25[6]	Median bite lesion size (loratadine) 16 mm^2 (range 0 to 288 mm^2); Median bite lesion size (placebo) 15 mm^2 (range 0 to 840 mm^2); NS reduction in bite lesion size with loratadine (p=0.53)[7]		⊕OOO VERY LOW	CRITICAL
Bite lesion size (follow-up 6 hours; measured with: loratadine versus placebo; Better indicated by lower values)												
1[1]	randomised trials[2]	serious [11]	not applicable	serious[3]	serious[4]	none	25[5]	25[6]	Median bite lesion size (loratadine) 9 mm^2 (range 0 to 625 mm^2); Median bite lesion size (placebo) 20 mm^2 (range 0 to 1360 mm^2); NS reduction in bite lesion size with loratadine (p=0.14)[7]		⊕OOO VERY LOW	CRITICAL
Bite lesion size (follow-up 24 hours; measured with: loratadine versus placebo; Better indicated by lower values)												
1[1]	randomised trials[2]	serious [11]	not applicable	serious[3]	serious[4]	none	25[5]	25[6]	Median bite lesion size (loratadine) 36 mm^2 (range 0 to 1600 mm^2); Median bite lesion size (placebo) 49 mm^2 (range 16 to 2500 mm^2); 27% reduction in bite lesion size with loratadine (p=0.004)[7]		⊕OOO VERY LOW	CRITICAL
Pruritus[8] (follow-up 15 minutes; measured with: loratadine versus placebo; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Loratadine	Placebo	Relative (95% CI)	Absolute		
1[1]	randomised trials[2]	serious [11]	not applicable	serious[3]	serious[4]	none	12[5]	12[6]	Median VAS for pruritus (loratadine) 10 (range 0 to 75); Median VAS for pruritus (placebo) 45 (range 0 to 90); 78% reduction in VAS for pruritus with loratadine (p=0.011)[7]		⊕OOO VERY LOW	CRITICAL
Adverse effects of mild gastrointestinal pain and diarrhoea (follow-up time period not reported; assessed with: loratadine versus placebo)												
1[1]	randomised trials[2]	no serious risk of bias	not applicable	serious[3]	very serious[9]	none	2/25 (8%)	0/25 (0%)	RR 5.00 (0.25 to 99.16)[10]	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; NS, Not statistically significant result; VAS, Visual analogue scale; RR, Relative risk.												

[1] Foex et al 2006 systematic review (additional information on effects size and adverse effects taken from included RCT papers)
[2] Double-blind, cross over trial
[3] Downgraded 1 level - population were people who were mosquito bite sensitive, with bite exposure but without infection
[4] Downgraded 1 level - not re-calculable, medians and range only
[5] Loratadine 0.3 mg/Kg (1 mg/mL mixture in 120 ml bottle) given daily at 08:00 am for 4 days (3 day washout period), then placebo for 4 days
[6] Placebo mixture (mixture in 120 ml bottle) given daily at 08:00 am for 4 days (3 day washout period), then Loratadine 0.3 mg/Kg (1 mg/mL mixture in 120 ml bottle for 4 days
[7] Wilcoxon's signed rank test with exact P value
[8] Pruritus was evaluated using a 100-mm visual analogue scale (VAS) ranging from 0 (no pruritus) to 100 (very intense pruritus)
[9] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with loratadine, and no meaningful difference or appreciable benefit with placebo, also very wide 95% confidence intervals (0.25 to 99.16)
[10] NICE analysis
[11] Downgraded 1 level- serious risk of bias because non-parametric statistics used which lack power and are inappropriate.

G.4 Treatments for people with an uninfected brown recluse spider bite

Table 13: GRADE profile – Interventions for loxosceles spider bites

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions	Control			
Number of patients developing necrotic lesions (follow-up time period not reported; assessed with prophylactic antibiotics, RICE, steroids, antihistamines and NSAIDs[1])											
1[2]	observational studies[3]	serious[4]	not applicable	serious[5]	serious[6]	none	52/52 (100%)[7]	-	n=9 (17.3%) with severe lesions (grade 3) n=43 (82.7%) with moderate lesions (grade 2) n=0 (0.0%) with mild lesions (grade 1)	⊕OOO VERY LOW	CRITICAL
Time to lesion healing (follow-up 0 to >8 weeks; measured with prophylactic antibiotics, RICE, steroids, antihistamines and NSAIDs; better indicated by lower values)											

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions	Control			
1[2]	observational studies[3]	serious[4]	not applicable	serious[5]	serious[6]	none	52[7]	-	Overall, time to healing ranged from 14 days to >8 weeks (mean 4.8 weeks) Average time[8] to healing for grade 3 lesions was 82 days Average time[8] to healing for grade 2 lesions was 38 days	⊕OOO VERY LOW	CRITICAL
Length of hospital stay (measured with prophylactic antibiotics, RICE, steroids, antihistamines and NSAIDs; better indicated by lower values)											
1[2]	observational studies[3]	serious[4]	not applicable	serious[5]	serious[6]	none	52[7]	-	57.7% of patients were hospitalised for >2 days Length of stay was significantly longer for patients with grade 3 lesions on the thigh (p<0.02)	⊕OOO VERY LOW	IMPORTANT
Abbreviations: RICE, Rest Ice Compression and Elevation; NSAID, Non-steroidal anti-inflammatory drug.											

[1] Not all patients received all medications
[2] Dyachenko et al 2006
[3] Case series
[4] Downgraded 1 level - retrospective study of 52 cases of presumed or definite brown recluse spider bites. Inclusion criteria are given but not reported if or how many potential cases were not included or if the cases are consecutive
[5] Downgraded 1 level – all patients had presumed or definite brown recluse spider bites but there are no reports of secondary infection
[6] Downgraded 1 level - lack of control in observational case series means no opportunity to assess
[7] All patients treated with rest, elevation, cold compresses and prophylactic systemic antibiotics to prevent secondary infection (mostly cephalexin 92.3% dose and duration not reported). All patients also received topical antibiotics (medicine name, dose and duration not reported). Most patients also received steroids (prednisolone 92.3% dose and duration not reported) and antihistamines (92.3% medicine name, dose and duration not reported). Twenty one of 52 patients (40.4%) also received non-steroidal anti-inflammatory medication (medicine name, dose and duration not reported)
[8] Unclear if mean or median reported

Appendix H: Excluded studies

Study reference	Reason for exclusion
Anonymous (2012) Management of simple insect bites: where's the evidence? *Drug and therapeutics bulletin* 50(4), 45-8	Study type – not a systematic review or RCT
Bernardeschi C, Cleach LL, Delaunay P et al (2013) Bed bug infestation. *BMJ* (Online) 346(7892), f138	Study type – not a systematic review or RCT
Botelho-Nevers E, Socolovschi C, Raoult D et al (2012) Treatment of Rickettsia spp. infections: A review. *Expert Review of Anti-Infective Therapy* 10(12), 1425-1437	Incorrect population – rickettsia is out-of-scope
Brown SA, Seifert SA, Rayburn WF (2013) Management of envenomations during pregnancy. *Clinical Toxicology* 51(1), 3-15	Insufficient clinical outcomes reported
Carlson J and Golden DBK (2016) Large local reactions to insect envenomation. *Current opinion in allergy and clinical immunology* 16(4), 366-9	Study type – not a systematic review or RCT
Diaz JH (2016) Tickborne Coinfections in the United States. *The Journal of the Louisiana State Medical Society: official organ of the Louisiana State Medical Society* 168(2), 44-53	Insufficient clinical outcomes reported
Eldin C and Parola P (2018) Update on Tick-Borne Bacterial Diseases in Travelers. *Current infectious disease reports* 20(7), 17	Study type – not a systematic review or RCT
Forks TP (2000) Brown recluse spider bites. *The Journal of the American Board of Family Practice* 13(6), 415-23	Not best evidence available as a more recent systematic review is included
Goddard J and deShazo R (2009) Bed Bugs (Cimex lectularius) and Clinical Consequences of Their Bites. Journal of the American Medical Association. April 1. 301(13). Pages 1358 to 1366	Insufficient clinical outcomes reported
Hockenhull J, Elremeli M, Cherry MG et al (2012) A systematic review of the clinical effectiveness and cost effectiveness of Pharmalgen for the treatment of bee and wasp venom allergy. *Health Technology Assessment* 16(12), I-109	Intervention (for anaphylaxis) is out-of-scope
Karppinen A, Kautiainen H, Reunala T, Petman L, Reunala T, and Brummer-Korvenkontio H (2000) Loratadine in the treatment of mosquito-bite-sensitive children. *Allergy* 55(7), 668-71	Not best evidence available as a more recent systematic review is included
Karppinen A, Kautiainen H, Petman L, Burri P, and Reunala T (2002) Comparison of cetirizine, ebastine and loratadine in the treatment of immediate mosquito-bite allergy. Allergy: European *Journal of Allergy and Clinical Immunology* 57(6), 534-537	Not best evidence available as a more recent systematic review is included
Karppinen A, Rantala I, Vaalasti A, Palosuo T, and Reunala T (1996) Effect of cetirizine on the inflammatory cells in mosquito bites. *Clinical and experimental allergy* 26(6), 703-709	Excluded on publication date (pre year 2000)
Karthikeyan K and Kumar A (2017) Paederus dermatitis. *Indian journal of dermatology, and venereology and leprology* 83(4), 424-431	Incorrect population – paederus dermatitis is out-of-scope
Modjtahedi BS, Modjtahedi SP, Mansury AM et al (2006) Mosquito bite therapy: Evidenced-based. *Exogenous Dermatology* 3(6), 332-338	Not best evidence available as another systematic review included additional RCTs
Pauli I, Puka J, Gubert IC et al (2006) The efficacy of antivenom in loxoscelism treatment. *Toxicon* 48(2), 123-137	Study type – not a systematic review or RCT
Przybilla B and Ruëff F (2012) Insect stings: clinical features and management. *Deutsches Arzteblatt international* 109(13), 238-248	Study type – not a systematic review or RCT

Study reference	Reason for exclusion
Rahmani F, Banan K, Seyed M et al (2014) Poisonous Spiders: Bites, Symptoms, and Treatment; an Educational Review. *Emergency* (Tehran, and Iran) 2(2), 54-8	Study type – not a systematic review or RCT
Richardson M (2004) Causes and effective management of insect bites in the UK. *Nursing times* 100(22), 63-67	Study type – not a systematic review or RCT
Roos TC, Alam M, Ross S et al (2001) Pharmacotherapy of ectoparasitic infections. *Drugs* 61(8), 1067-1088	Intervention (aimed at removing parasite) not treating bites
Swanson D L, and Vetter R S (2005) Medical progress: Bites of brown recluse spiders and suspected necrotic arachnidism. New England Journal of Medicine 352(7), 700-707	Study type – not a systematic review or RCT
Tutrone WD, Green KM, Norris T et al (2005) Brown recluse spider envenomation: dermatologic application of hyperbaric oxygen therapy. Journal of drugs in dermatology: JDD 4(4), 424-8	Intervention (hyperbaric oxygen therapy) is out-of-scope