National Institute for Health and Care Excellence

APG human and animal bites: draft

Human and animal bites: antimicrobial prescribing guideline

Evidence review

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Draft for consultation

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1 Context

1.1 Background

A bite injury inflicted by the teeth of a human or animal can take a number of forms including lacerations, puncture wounds, and crush or degloving injuries. The most common mammalian bites are associated with humans, dogs, and cats, which may cause bruising, deep anatomical structure disruption and infections. Human bites can be deliberate, accidental or self-inflicted and are either caused by actual biting (occlusal injuries) or when a clenched fist hits a person's teeth causing small wounds over the hands (clenched-fist injuries). Most human bites occur on the hand. Dog bites generally involve puncture wounds from the canine teeth which anchor the victim, with other teeth biting, sheering and tearing tissues. They vary in severity depending on the type and size of dog. Cats have a weaker bite than dogs but inflict deep puncture wounds inoculated with saliva. Cat bites are capable of penetrating bone, joints and tendons, and infections such as abscesses and osteomyelitis are more common. The incidence of bites is likely to be underestimated because some people will not seek medical assistance or report them. However, dog bites are most common, followed by cat bites and human bites. It is estimated that approximately 250,000 people attend minor injury and accident and emergency departments in the UK each year for the treatment of dog bites (NICE clinical knowledge summary: Bites – human and animal [2018]).

Bites can result in bacterial infection if there is a break in the skin. The risk of infection is higher in areas of poor perfusion, where the wound is deep or contaminated, where there has been significant tissue damage, where bites have occurred on the hands, feet, face or genitals, or where they involve bone, joint or tendons. The type of bite injury, individual patient risk factors such as being immunocompromised, and the animal species causing the bite are also factors in the development of infection. Infective complications from bite injuries include abscesses (collection of pus that has built up within the tissue of the body), tenosynovitis (inflammation of the fluid-filled sheath that surrounds a tendon), septic arthritis (inflammation of a joint caused by a bacterial infection), osteomyelitis (bone infection) and systemic spread, such as sepsis. The longer an infected bite wound is untreated, the more likely severe local and systemic complications are to occur (NICE clinical knowledge summary: Bites – human and animal [2018]). The likely causative organisms of bacterial infection from a human bite differ from that of an animal bite. Human bites are most commonly infected by Streptococcus, *Staphylococcus aureus*, Haemophilus, *Eikenella corrodens*, Bacteroides and other anaerobes (NICE clinical knowledge summary: Bites – human and animal [2018]). Most infections from an animal bite are polymicrobial containing both aerobic and anaerobic organisms, with causative organisms for infections from dog and cat bites including Pasteurella, Streptococcus, Staphylococcus, Neisseria, Corynebacterium, *Fusobacterium nucleatum* and Bacteroides. (Abrahamian et al 2011).

The NICE clinical knowledge summary on Bites – human and animal provides advice on assessing, documenting and examining human and animal bites. It suggests that people who have been bitten should have how and when the bite occurred documented, vital signs monitored, especially if the bite is particularly traumatic, and the bite examined, with findings documented. The wound should have foreign bodies removed, it should be encouraged to bleed if not bleeding already, irrigated with warm running water, and considered for debridement or closure as appropriate (with referral to accident and emergency if required). The risk of infection should be assessed based on the type of animal, the nature of the bite, the site of injury, wound penetration, the length of delay in bite presentation, the age of the person receiving the bite and any associated medical conditions (NICE 2018).

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. This guideline also recommends that safety netting advice should be given to everyone who has an infection (regardless of whether or not they are prescribed or supplied with antimicrobials). This should include: how long symptoms are likely to last with and without antimicrobials, what to do if symptoms get worse, what to do if they experience adverse effects from the treatment, and when they should ask again for medical advice.

Public Health England guidance (Start Smart Then Focus) and the NICE guideline on antimicrobial stewardship consider reviewing intravenous antibiotic prescriptions 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 people
- 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 people 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). However due to the wide and varied bacteria

present in the mouth of animals and humans the use of broader spectrum antibiotics may be appropriate.

The ESPAUR report 2018 reported that antimicrobial prescribing declined significantly between 2013 and 2017, with the total consumption of antibiotics in primary and secondary care declining by 4.5%. This reflected a 13.2% decrease in primary care and a 7.7% increase in secondary care prescribing. The peak of antibiotic consumption over the last 20 years occurred in 2014, with levels falling since then. The most commonly used antibiotics in England remained stable between 2013 and 2017 and were: penicillins (44.6% in 2017), tetracyclines (22.2% in 2017) and macrolides (14.7% in 2017).

Over the 5-year period, significant declining trends of use were seen for penicillins (inhibitor combinations only), first and second-generation cephalosporins, sulfonamides and trimethoprim, and anti-*Clostridium difficile* agents. In contrast, use of third, fourth and fifth-generation cephalosporins and other antibacterials (including nitrofurantoin) significantly increased.

In the 5-year period from 2013 to 2017, primary care use of penicillins declined by 10.9%, with use of penicillins in the dental setting remaining largely the same. In the hospital setting, prescribing of penicillins was higher in 2017 for both inpatients (2.4%) and outpatients (14.7%) compared with 2013. Prescribing of co-amoxiclav, amoxicillin and piperacillin with tazobactam between 2013 and 2017 decreased by 11.3%, 7.4% and 30.2% respectively.

The use of cephalosporins has decreased by 21.4% due to reductions within primary care and is attributed to a decline in the use of cefalexin. However, the observed rate between 2016 and 2017 for cephalosporins overall remained unchanged.

Overall use of tetracyclines was unchanged between 2013 and 2017, with doxycycline (49.7% in 2017) and lymecycline (36.3% in 2017) most commonly used. Macrolide use declined by 5.8% from 2013 to 2017. Azithromycin use continued to increase in 2017, with overall use rising by 31.3% since 2013. In contrast, erythromycin use declined over the same period by 40.7%.

Between 2013 and 2017 fluoroquinolone use remained broadly stable but there was a 14.5% decline in use in primary care over the same period. Ciprofloxacin, norfloxacin and ofloxacin prescriptions have all declined from 2013 to 2017, but levofloxacin use increased by 98.0%.

The use of glycopeptides (vancomycin, teicoplanin and daptomycin) occurred almost exclusively in hospitals and most commonly in inpatients, with prescribing increasing by 40.1% over the 5-year period from 2013 to 2017.

Carbapenem use in secondary care remained stable from 2013 to 2017, but acute trusts and specialist and teaching trusts increased their use by 24.0% and 3.6%, respectively, between 2016 and 2017. A decline in use was seen in multiservice, small, medium and large trusts.

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.

2.1 Literature search

A literature search was developed to identify evidence for the effectiveness and safety of interventions for managing animal and human bites (see appendix C: literature search strategy for full details).

The literature search identified 1668 references. These references were screened using their titles and abstracts and 91 full text references were obtained and assessed for relevance with 5 full texts unable to be retrieved. One full text reference of a systematic review and 2 full text references of randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix B: review protocol). Ten 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 (see appendix F: included studies).

The 88 studies that were excluded are listed in appendix I: excluded studies, with reasons for exclusion. No studies were deprioritised.

See also appendix D: study flow diagram.

2.2 Summary of included studies

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

Table 1: Summary of included studies: antibiotic efficacy (prophylactic)

Study	Number of participants	Population[1]	Intervention	Comparison	Primary outcome[2]
Prophylactic antibiotic versus placebo (all bites)					
Medeiros et al 2001 SR Worldwide	8 RCTs n=522	Adults and children with mammalian (dogs and cats) or human bites attending within 12-24 hours of injury[3]	Prophylactic antibiotic[4] for between 5 to 7 days	No antibiotic/placebo	Incidence of infection
Prophylactic antibiotic versus placebo (dogs)					
Medeiros et al 2001 SR Worldwide	6 RCTs n=463	Adults and children with dog bites attending within 12-24 hours of injury[3]	Prophylactic antibiotic for between 2 and 7 days[3]	No antibiotic/placebo	Incidence of infection
Quinn et al 2009 RCT USA	1 RCT n=94	People with an uninfected dog bite attending within 12 hours of injury	Prophylactic antibiotic (oral co-amoxiclav) for 3 days	Placebo	Incidence of infection
Prophylactic antibiotic versus placebo (cats)					
Medeiros et al 2001 SR Worldwide	1 RCT n=11	Adults with cat bites attending within 24 hours of injury, without clinical signs of infection	Prophylactic antibiotic (oxacillin) for 5 days	Placebo	Incidence of infection
Prophylactic antibiotic versus placebo (humans)					
Medeiros et al 2001 SR Worldwide	1 RCT n=48	Adults with human bites attending within 24 hours of injury, without clinical signs of infection	Prophylactic antibiotic (oral cefaclor, IV cefazolin or IV benzylpenicillin), duration not reported.	Placebo	Incidence of infection
Broder et al 2004 RCT USA	1 RCT n=127	Adults with low-risk human bites attending within 24 hours of injury	Prophylactic antibiotic (cefalexin/penicillin combination) for 5 days	Placebo	Incidence of infection

Study	Number of participants	Population[1]	Intervention	Comparison	Primary outcome[2]

[1]Broder et al (2004) describes study participants as having low-risk bites defined as 'penetrating only the epidermis and not involving hands, feet, skin overlying joints, or cartilaginous structures'. The risk status of bites was not specified in other studies. On review of the included studies in Medeiros et al (2001) SR and Quinn et al (2010) bites could be categorised as 'low-risk' in line with Broder et al (2004) definition with the exception of 3 studies within Medeiros et al (2001) review which focused on bites to the hand.

[2]Adverse events were not reported in any of the identified studies

[3]The included studies within the Mederios et al (2001) SR had a range of inclusion and exclusion criteria. Studies included participants if bites received did not penetrate a joint capsule or injured tendons, did not require closure with sutures, were non-facial, if people had no history of penicillin or co-trimoxazole allergy and if no antibiotics were being administered at the time of the bite. Some studies within the SR excluded participants if bites were to the hand or foot, or if there were puncture wounds, if there were clinical signs of infection, a history of immunosuppression disorders or medications, if participants were <1 year old or if participants required hospitalisation.

[4]Prophylactic antibiotics included oral phenoxymethylpenicillin, IV benzylpenicillin, oral dicloxacillin, oral cefalexin, oral erythromycin, oxacillin, co-trimoxazole, cloxacillin, oral cefaclor or IV cefazolin

Abbreviations: IV, intravenous; RCT, randomised controlled trial; SR, systematic review

3 Evidence summary

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

The main results are summarised below for adults, young people and children with a human and animal bite. The evidence identified focused exclusively on antibiotic prophylaxis. 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

3.1.1 Antibiotic efficacy in adults, young people and children

3.1.1.1 Antibiotic prophylaxis versus no antibiotic prophylaxis or placebo

The evidence review for antibiotic prophylaxis compared with no antibiotic prophylaxis or placebo is based on 1 systematic review in adults, young people and children who had received a mammalian (human, dog or cat) bite (Medeiros et al. 2001), and 2 further RCTs (Broder et al. 2004; Quinn et al. 2010) that considered human and dog bites respectively.

Medeiros et al (2001) undertook stratification of the results and presented them by animal, by wound type and location of wound. These results are reported below. Broder et al (2004) and Quinn et al (2010) did not stratify their results in this manner and only presented results by animal type .

Broder et al (2004) included participants with low-risk bites, the risk status of participants bites was not specified in Medeiros et al (2001) or Quinn et al (2010). However 3 RCTs included in the Medeiros et al (2001) systematic review included participants who had received bites to the hand: 1 which focused on hand bites from humans and 2 sub-groups within 2 RCTs which focused on hand bites from dogs, making them potentially at higher risk of infection. The findings of these high-risk bites are stratified within the Medeiros et al (2001) systematic review and presented in this review in the section on hand bites. This review further stratifies the high-risk hand bite findings by animal and these are presented within the human bites and dog bites sections respectively.

Human and animal bites (pooled)

The evidence for antibiotic prophylaxis compared with no antibiotic prophylaxis or placebo for human and animal bites comes from 1 systematic review (Medeiros et al. 2001) and 2 RCTs (Broder et al. 2004; Quinn et al. 2010) in a total of 741 adults, young people and children with injuries caused by dogs, cats or humans.

Overall, the pooled analysis indicated that there was no significant difference between the prophylactic antibiotic group and the no prophylactic antibiotic or placebo group for incidence of infection (n=741, 2.7% vs 8.0%; RR 0.46 95% CI 0.20 to 1.07; NICE analysis, low quality evidence). Sensitivity analysis of high risk bites indicated no significant difference between prophylactic antibiotics and placebo for incidence of infection (n=104, 1.6% versus 27.9%; RR 0.16, 95% CI 0.02 to 1.17; NICE analysis). These bites all occurred on the hand and are also outlined in the section on hand bites. Sensitivity analysis of low-risk bites indicated no significant

difference between prophylactic antibiotics and placebo for the incidence of infection (n=637, 2.9% versus 5.6%; RR 0.62, 95% CI 0.28 to 1.37; NICE analysis).

Antibiotic prophylaxis regimens varied across the RCTs and included oral phenoxymethylpenicillin, intravenous (IV) benzylpenicillin, oral dicloxacillin, oral cefalexin, oral erythromycin, oxacillin, co-trimoxazole, cloxacillin, oral cefaclor, IV cefazolin, oral cefalexin/penicillin combination and oral co-amoxiclav taken for between 2 and 7 days. The location of the bite (trunk, head or neck, hands or arms, or not outlined), the type of bite (puncture, laceration, avulsion or not outlined) varied. For this review, a pooled analysis and a sensitivity analysis for high- and low-risk bites was undertaken.

There was a lack of detail regarding the demographics of participants within the included studies and the specific methodological procedures undertaken. Some of the studies specifically excluded participants on the presence of infection and the risk posed by the bite by its severity and location for example, if it required closure with sutures, penetrated a joint capsule or occurred on the face.

See GRADE profiles: Table 4.

Dog bites

The evidence for antibiotic prophylaxis compared with no antibiotic prophylaxis or placebo for dog bites comes from 1 systematic review (Medeiros et al. 2001), and 1 RCT (Quinn et al. 2010) in adults and children with injuries caused by dogs.

Overall, there was no significant difference between the prophylactic antibiotic group and the no prophylactic antibiotic or placebo group for incidence of infection (n=557, 3.7% versus 6.0%; RR 0.64, 95% CI 0.28 to 1.45; NICE analysis, very low quality evidence). Sensitivity analysis of high-risk dog bites (dog bites to the hand) indicated no significant difference between prophylactic antibiotics (co-trimoxazole [method and duration of treatment not outlined] or oral phenoxymethylpenicillin 100,000 U/Kg/day given every 6 hours for 2 days) and placebo (n=56, 3.6% versus 17.9%; RR 0.35, 95% CI 0.05 to 2.55, NICE analysis). Sensitivity analysis of low-risk dog bites (dog bites not to the hand) indicated no significant difference between prophylactic antibiotics (oral phenoxymethylpenicillin 250 mg four times a day or 100,000 U/Kg/day given every 6 hours for 2 days, oral dicloxacillin 250 mg to 500 mg four times a day, oxacillin 500 mg four times a day, oral cefalexin 500 mg four times a day, oral erythromycin 500 mg four times a day, co-trimoxazole [dose not outlined], cloxacillin 250 mg four times a day or oral co-amoxiclav [dose not outlined] taken for between 3 to 7 days) and placebo (n=501, 3.7% versus 4.7%; RR 0.82, 95% CI 0.34 to 1.96, NICE analysis)

Antibiotic prophylaxis regimens varied and included oral phenoxymethylpenicillin 250 mg four times a day or 100,000 U/Kg/day given every 6 hours for 2 days, oral dicloxacillin 250 mg to 500 mg four times a day, oxacillin 500 mg four times a day, oral cefalexin 500 mg four times a day, oral erythromycin 500 mg four times a day, co-trimoxazole (dose not outlined), cloxacillin 250 mg four times a day or oral co-amoxiclav (dose not outlined) taken for between 3 to 7 days. There was a lack of details regarding the demographics of participants and methodological procedures undertaken in some of the included studies. Some studies excluded participants by the severity and location of the dog bite for example if it required closure with sutures, involved bone or tendon or occurred on the hand. Follow-up was reported as 14 days in one study (Quinn et al. 2010) but this was not reported in the other studies within the systematic review (Medeiros et al. 2001).

See GRADE profiles: Table 5.

3.1.1.1.2 *Antibiotic prophylaxis versus placebo for the treatment of cat bites*

The evidence for antibiotic prophylaxis compared with placebo for cat bites comes from 1 systematic review (Mederios et al. 2001) in adults with injuries caused by cats without clinical signs of infection.

The study included 12 adults who were randomised to antibiotic prophylaxis with oxacillin 500 mg four times a day for 5 days or placebo. Overall, there was no significant difference between the prophylactic antibiotic group (oxacillin 500 mg four times a day for 5 days) and the placebo group for incidence of infection (n=11, 0% versus 66.7%; RR 0.13, 95% CI 0.01 to 1.95; NICE analysis, very low quality evidence).

The location of the bite was not outlined but the study did report that it included full-thickness injuries. Participants were excluded if there were signs of infection, if the injury required hospitalisation, or if there was violation of the periosteum (vascular connective tissue enveloping the bones except at the surfaces of the joints). There was a lack of detail regarding the demographics of participants within the study and the specific methodological procedures undertaken.

See GRADE profiles: Table 6.

3.1.1.1.3 *Human bites*

The evidence for antibiotic prophylaxis compared with placebo for the treatment of human bites is based on 1 systematic review (Medeiros et al. 2001), and 1 further randomised controlled trial (RCT) of 127 adults (Broder et al. 2004) who had received a human bite.

A pooled analysis of 1 systematic review (Medeiros et al. 2001) and 1 RCT (Broder et al. 2004) compared antibiotic prophylaxis with placebo in 173 adults who had been bitten by a human. Overall, prophylactic antibiotics significantly reduced the incidence of infection compared with placebo (n=173, 0% versus 10.4%; RR 0.09, 95% CI 0.01 to 0.92, number needed to treat [NNT] 10; NICE analysis, low quality evidence). Broder et al (2004) considered low-risk human bites and Medeiros et al (2001) considered human bites to the hand, which are considered to be at higher risk of infection due to site of the bite. A sensitivity analysis was undertaken on high and low risk bites, there was no significant difference between prophylactic antibiotics and placebo for incidence of infection in low-risk human bites (n=125, 0% versus 1.6%; RR 0.33; 95% CI 0.01 to 7.90; NICE analysis) but Medeiros et al (2001) did demonstrate a significant difference between prophylactic antibiotics and placebo for incidence of infection in high-risk human bites (n=24; 0% versus 46.7%; RR 0.03 95% CI 0.00 to 0.52; NNT 2; NICE analysis, moderate quality evidence)

Antibiotic prophylaxis regimens varied and included oral cefaclor 250 mg three times a day (duration not outlined), IV cefazolin 1 g four times a day (duration not outlined), IV benzylpenicillin 1.2 million units four times a day (duration not outlined) or oral cefalexin/penicillin combination (dose not outlined) for 5 days. Bites to the hand were included in 1 study (Medeiros et al. 2001) but all bites across the pooled analysis did not penetrate a joint capsule, injure a tendon or cartilaginous structures. There was a lack of details regarding the demographics of participants in both studies and a lack of the specific methodological procedures undertaken within 1 study (Medeiros et al. 2001). One study (Broder et al. 2004) asked people to return at 48 and 96 hours after their initial visit to be assessed for signs of infection.

See GRADE profiles: Table 7.

3.1.1.1.4 Antibiotic efficacy: stratification by wound type

Mederios et al. (2001) stratified studies where bites were classified by wound type: puncture, laceration and avulsion. These comparisons by wound type use the same data that informs comparisons of antibiotic prophylaxis versus no antibiotic prophylaxis or placebo for human, dog and cat bites. The primary outcome across all studies was the incidence of infection. The comparisons by wound type are based on 1 systematic review.

Puncture wounds

One systematic review (n=30) randomised adults, young people and children to either antibiotic prophylaxis (oxacillin 500 mg four times a day for 5 days or oral phenoxymethylpenicillin 100,000 U/kg/day given every 6 hours for 2 days) or placebo. There was a lack of details regarding the demographics of participants within the systematic review and the specific methodological procedures undertaken in the RCTs.

Overall, there was no significant difference between prophylactic antibiotics and placebo for incidence of infection in puncture wound bites (n=30, 7.1% versus 31.3%; RR 0.38, 95% CI 0.03 to 4.13; NICE analysis, very low quality evidence).

Laceration wounds

One systematic review (n=129) randomised adults, young people and children to either antibiotic prophylaxis (oral dicloxacillin or oral cefalexin or oral erythromycin 500 mg four times a day [50 mg/kg/day for children] for 7 days or oral phenoxymethylpenicillin 100,000 U/kg/day given every 6 hours for 2 days) or placebo. There was a lack of details regarding the demographics of participants within the systematic review and the specific methodological procedures undertaken in the RCTs.

Overall, there was no significant difference between prophylactic antibiotics and placebo for incidence of infection in laceration wound bites (n=129, 3.2% versus 6.1%; RR 0.79, 95% CI 0.06 to 11.03; NICE analysis, very low quality evidence).

Avulsion wounds

One systematic review (n=71) which randomised adults, young people and children to either antibiotic prophylaxis (oral dicloxacillin or oral cefalexin or oral erythromycin 500 mg four times a day [50 mg/kg/day for children] for 7 days or oxacillin 500 mg four times a day for 5 days) or placebo. There was a lack of details regarding the demographics of participants within the systematic review and the specific methodological procedures undertaken in the RCTs.

Overall, there was no significant difference between prophylactic antibiotics and placebo for incidence of infection in avulsion wound bites (n=71, 4.9% versus 3.3%; RR 1.06, 95% CI 0.12 to 9.24; NICE analysis, very low quality evidence).

See GRADE profiles: Table 8.

3.1.1.1.5 Antibiotic efficacy: stratification by wound site

Mederios et al. (2001) stratified studies where bites were classified by wound site: trunk, head and neck, hands, and arms. These comparisons by wound site use the same data that informs comparisons of antibiotic prophylaxis versus no antibiotic prophylaxis or placebo for human, dog and cat bites. The primary outcome across all

studies was the incidence of infection. The comparisons by wound type are based on 1 systematic review.

Trunk wounds

One systematic review (n=32) randomised adults, young people and children to either antibiotic prophylaxis (oral dicloxacillin or oral cefalexin or oral erythromycin 500 mg four times a day [50 mg/kg/day for children] for 7 days or oral phenoxymethylpenicillin 100,000 U/kg/day given every 6 hours for 2 days) or placebo. There was a lack of details regarding the demographics of participants within the systematic review and the specific methodological procedures undertaken in the RCTs.

Overall, there was no significant difference between prophylactic antibiotics and placebo for incidence of infection in bites occurring on the trunk (n=32, 6.7% versus 0%; RR 1.50, 95% CI 0.10 to 22.62; NICE analysis, very low quality evidence).

Head and neck wounds

One systematic review (n=82) randomised adults, young people and children to either antibiotic prophylaxis (oral dicloxacillin or oral cefalexin or oral erythromycin 500 mg four times a day [50 mg/kg/day for children] for 7 days or oral phenoxymethylpenicillin 100,000 U/kg/ day given every 6 hours for 2 days) or placebo. There was a lack of details regarding the demographics of participants within the systematic review and the specific methodological procedures undertaken in the RCTs.

Overall, there was no significant difference between prophylactic antibiotics and placebo for incidence of infection in bites occurring on the head and neck (n=82, 0% versus 2.4%; RR 0.32, 95% CI 0.01 to 7.48; NICE analysis, very low quality evidence).

Hand wounds

One systematic review (n=104) randomised adults, young people and children to either antibiotic prophylaxis (co-trimoxazole [regimen not specified] or oral phenoxymethylpenicillin 100,000 U/Kg/day given every 6 hours for 2 days or oral cefaclor 250 mg three times a day or IV cefazolin 1 g four times a day or IV benzylpenicillin 1.2 million units four times a day [duration not specified]) or placebo. There was a lack of details regarding the demographics of participants within the systematic review and the specific methodological procedures undertaken in the RCTs.

Overall, there was no significant difference between prophylactic antibiotics and placebo for incidence of infection in bites occurring on the hand (n=104, 1.6% versus 27.9%; RR 0.16, 95% CI 0.02 to 1.17; NICE analysis, low quality evidence).

Arm wounds

One systematic review (n=5) randomised adults, young people and children to either antibiotic prophylaxis (oral phenoxymethylpenicillin 100,000 U/Kg/day given every 6 hours for 2 days) or placebo. There was a lack of details regarding the demographics of participants within the systematic review and the specific methodological procedures undertaken in the RCT.

There was no incidence of infection in either arm of the study and as such prophylactic antibiotics demonstrated no significant effect compared with placebo for incidence of infection in bites occurring on the arm (n=5, 0% versus 0%; not estimable; very low quality).

See GRADE profiles: Table 9.

3.16.2 Choice of antibiotic in adults, young people and children

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.18.3 Antibiotic course length in adults, young people and children

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.10.4 Antibiotic route of administration in adults, young people and children

No systematic reviews or randomised controlled trials met the inclusion criteria.

4 Terms used in the guideline

Low-risk bites

Low-risk bites are defined as bites that only penetrating the epidermis and do not involving hands, feet, skin, overlying joints, or cartilaginous structures (Broder et al 2004)

High-risk bites

The risk of infection is high in deep or contaminated wounds; injuries with significant tissue destruction; in areas of poor perfusion; bites affecting the hands, feet, face, and genitals; and where there is bone, joint, or tendon involvement (NICE clinical knowledge summary: Bites – human and animal [2018]) .

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?	• CKS - Bites – human and animal - NICE 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)?	• NICE guideline NG63: NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • Committee experience
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 (2018)
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• NHSBSA Drug Tariff

Key area	Key question(s)	Evidence sources
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• NICE guideline NG76: Medicines adherence: involving people 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) • BNF for children (BNF-C) • Summary of product characteristics

1
2

Appendix B: Review protocol

Review question	What antimicrobial interventions are effective in managing human and animal bites?
Types of review question	Intervention
Objective of the review	To determine the effectiveness of prescribing interventions in managing infections caused by bites from humans or animals to address antimicrobial resistance. In line with the major 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 a human and/or animal.
Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	The review will include studies which include: Antimicrobial pharmacological interventions[1]. For the treatment of animal and/or human 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.

1 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

	Non-antimicrobial pharmacological interventions. Other antimicrobial pharmacological interventions.
Outcomes and prioritisation	Infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) Time to clinical cure (mean or median time to resolution of illness) Reduction in symptoms (duration or severity) Rate of complications with or without treatment Safety, tolerability, and adverse effects. Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. Service user experience. Health and social care related quality of life, including long-term harm or disability. 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: • non-randomised controlled trials • systematic reviews of non-randomised controlled trials • cohort studies • before and after studies

	• interrupted 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 and narrative reviews in relation to antimicrobial resistance, non-UK papers antimicrobials that are not available in the UK non-pharmacological interventions or non-antimicrobial pharmacological interventions Rabies, tetanus, HIV and hepatitis are excluded from this guideline Use of antimicrobial pharmacological interventions[2] to offset the impacts of anti-venom are excluded. other treatments for example anti-venom
Proposed sensitivity/ sub-group analysis, or meta-regression	Subgroups, where possible, will include: • population subgroups (for example adults, older adults, children (those aged under 18 years of age) • people with co-morbidities people with characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment.
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.

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

	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 CRD – legacy database, last updated April 2015 • Embase via Ovid • Health Technology Assessment (HTA) via CRD • 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	This is a new protocol.
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	Study checklists were used to critically appraise individual studies. For details please see appendix H of Developing NICE guidelines: the manual The following checklists will be used: Risk of bias of intervention studies - systematic reviews and meta-analyses will be assessed using the Risk of Bias in Systematic Reviews (ROBIS) checklist

	Risk of bias of intervention studies – randomised controlled trials (individual or cluster) will be assessed using the Cochrane risk of bias (RoB) 2.0 tool Risk of bias of cohort studies will be assessed using Cochrane ROBINS-I. Risk of bias of single-arm observational studies will be assessed using the IHE Quality Appraisal Checklist for Case Series Studies. 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)	Results reported by individual studies will be reported in the evidence review in narrative format and in GRADE tables in appendix H of the evidence review. If systematic reviews are identified as being sufficiently applicable and high quality, they will be used as the primary source of data, rather than extracting information from primary studies. Where appropriate, meta-analyses may be conducted to combine the results of quantitative studies for each outcome, for example: • if there is concern about the reported data (for example, if statistical significance has not been reported or inappropriate methods have been used for meta-analysis), • if more than one study reports the same comparison and outcomes
Methods for analysis – combining studies and exploring (in)consistency	Where meta-anaysis is undertaken they will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) and they will be performed in Cochrane Review Manager.

	A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Both relative and absolute risks will be presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials). Fixed- and random-effects models (der Simonian and Laird) will be used, with the choice of model based on the degree of heterogeneity for the results of each outcome. Fixed-effects models are the preferred choice, but in situations where the assumptions of a shared mean for fixed-effects model are clearly not met, random-effects results will be presented. Random-effects models will be selected for analysis if significant statistical heterogeneity is identified in the meta-analysis, defined as $I^2 \geq 50\%$. Network meta-analysis (NMA) will not be carried out for antimicrobial prescribing guidelines. If a study that is included in the review has undertaken and NMA and reports these results, they will be reported verbatim in the evidence review.
Meta-bias assessment – publication bias, selective reporting bias	Where meta-analysis is undertaken, please see Developing NICE guidelines: the manual (2018) for details.
Assessment of confidence in cumulative evidence	Where meta-analysis is undertaken, please see Developing NICE guidelines: the manual (2018) for details. Information on medicines safety data and antimicrobial resistance will not be quality assessed.
Rationale/ context – Current management	For details please see the introduction to the evidence review in the main file.
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 Developing NICE guidelines: the manual (2018).

	Staff from NICE undertook systematic literature searches, appraised the evidence and conducted meta-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.

1

Appendix C: Literature search strategy

1 "bites and stings"/ (7305)
2 Bites, Human/ (1046)
3 (bite or bites or bitten* or biting*).ti,ab. (35178)
4 ((teeth* or tooth*) adj3 (knuckle* or hand or hands or finger* or thumb* or metacarpophalangeal* or metacarpus* or metacarpal* or carpal* or carpus* or phalange* or interphalangeal* or distalphalange*)).ti,ab. (295)
5 or/1-4 (39327)
6 Amikacin/ (3939)
7 Amikacin*.ti,ab. (8818)
8 exp Amoxicillin/ (10678)
9 Amoxicillin*.ti,ab. (13700)
10 Ampicillin/ (13181)
11 Ampicillin*.ti,ab. (21759)
12 Azithromycin/ (4651)
13 (Azithromycin* or Azithromicin* or Zithromax*).ti,ab. (7328)
14 Penicillin G/ (8959)
15 (Benzylpenicillin* or "Penicillin G").ti,ab. (8038)
16 (Ceftaroline* or Zinforo*).ti,ab. (589)
17 Clarithromycin/ (5944)
18 (Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab. (8513)
19 Chloramphenicol/ (19151)
20 (Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab. (25815)
21 Clindamycin/ (5496)
22 (Clindamycin* or Dalacin* or Zindaclin*).ti,ab. (9803)
23 Amoxicillin-Potassium Clavulanate Combination/ (2423)
24 (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. (14773)
25 Doxycycline/ (9074)
26 (Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab. (12345)
27 (Ertapenem* or Invanz*).ti,ab. (1337)
28 Erythromycin/ (13549)
29 Erythromycin Estolate/ (148)
30 Erythromycin Ethylsuccinate/ (514)
31 (Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab. (20089)
32 Floxacillin/ (705)
33 (Floxacillin* or Flucloxacillin*).ti,ab. (812)
34 Framycetin/ (495)
35 Framycetin*.ti,ab. (161)

36 Fusidic Acid/ (1562)
37 ("Fusidic acid" or fusidate* or Fucidin*).ti,ab. (1967)
38 Gentamicins/ (17757)
39 (Gentamicin* or Gentamycin* or Cidomycin*).ti,ab. (25534)
40 Imipenem/ (3888)
41 (Imipenem* or Primaxin*).ti,ab. (9730)
42 Levamisole/ (4249)
43 (Levamisole* or ergamisol*).ti,ab. (4438)
44 Levofloxacin/ (3018)
45 (Levofloxacin* or Evoxil* or Tavanic*).ti,ab. (6872)
46 Linezolid/ (2681)
47 (Linezolid* or Zyvox*).ti,ab. (5179)
48 Meropenem*.ti,ab. (5613)
49 Metronidazole/ (12224)
50 Metronidazole*.ti,ab. (14501)
51 exp Neomycin/ (9080)
52 (neom?cin* or "Neo-Fradin").ti,ab. (9287)
53 Mupirocin/ (1149)
54 (Mupirocin* or Bactroban*).ti,ab. (1667)
55 Ofloxacin/ (5912)
56 (Ofloxacin* or Tarivid*).ti,ab. (6575)
57 Penicillin V/ (2151)
58 (Phenoxymethylpenicillin* or "Penicillin V").ti,ab. (1507)
59 Piperacillin/ (2639)
60 (Piperacillin* or Tazobactam* or Tazocin*).ti,ab. (6914)
61 Teicoplanin/ (2173)
62 (Teicoplanin* or Targocid*).ti,ab. (3415)
63 Tedizolid*.ti,ab. (215)
64 (Tigecycline* or Tygacil*).ti,ab. (2749)
65 Vancomycin/ (12807)
66 (Vancomycin* or Vancomicin* or Vancocin*).ti,ab. (24952)
67 or/6-66 (247267)
68 5 and 67 (873)
69 exp Aminoglycosides/ (148610)
70 Aminoglycoside*.ti,ab. (17793)
71 exp Penicillins/ (78462)
72 Penicillin*.ti,ab. (52798)
73 exp beta-Lactamases/ (21398)
74 exp beta-Lactamase inhibitors/ (7347)
75 ((beta adj Lactamase*) or betaLactamase* or beta-Lactamase*).ti,ab. (25659)
76 beta-Lactams/ (6165)
77 (beta-Lactam or betaLactam or beta Lactam or beta-Lactams or betaLactams or beta Lactams).ti,ab. (19853)

78 exp Carbapenems/ (9871)
79 Carbapenem*.ti,ab. (12098)
80 exp Cephalosporins/ (40709)
81 Cephalosporin*.ti,ab. (20824)
82 exp Fluoroquinolones/ (30647)
83 Fluoroquinolone*.ti,ab. (15030)
84 exp Macrolides/ (103337)
85 macrolide*.ti,ab. (14720)
86 Polymyxins/ (2843)
87 Polymyxin*.ti,ab. (6753)
88 exp Quinolones/ (43985)
89 Quinolone*.ti,ab. (13094)
90 exp Tetracyclines/ (46229)
91 Tetracycline*.ti,ab. (33866)
92 or/69-91 (493463)
93 5 and 92 (1139)
94 Chlorhexidine/ (7731)
95 (Chlorhexidine* or Unisept* or Hibiscrub* or Hydrex* or Hibi or HiBiTane*).ti,ab. (9769)
96 ("Dialkylcarbamoyl chloride" or "Cutimed Sorbact").ti,ab. (18)
97 Glucose oxidase/ (4752)
98 "Glucose oxidase".ti,ab. (5870)
99 Hydrogen Peroxide/ (53495)
100 ("Hydrogen peroxide" or crystacide*).ti,ab. (48563)
101 Lactoperoxidase/ (1308)
102 (Lactoperoxidase* or Flaminal*).ti,ab. (2392)
103 (Octenidine* or Octenilin*).ti,ab. (246)
104 (Polihexanide* or Suprasorb* or Polyhexamethylene*).ti,ab. (506)
105 Povidone-Iodine/ (2652)
106 (Povidone-Iodine* or Betadine* or Videne* or Inadine*).ti,ab. (3159)
107 Potassium Permanganate/ (1524)
108 ("Potassium permanganate" or "EN-Potab" or Permitabs).ti,ab. (1573)
109 Proflavine/ (523)
110 Proflavine*.ti,ab. (638)
111 Silver Sulfadiazine/ (900)
112 (Silver Sulfadiazine* or Flamazine*).ti,ab. (908)
113 (reactive oxygen or surgihoney*).ti,ab. (104980)
114 Iodine/ (24439)
115 (Iodine* or Iodoflex* or Iodosorb* or Iodozyme* or Oxyzyme*).ti,ab. (45333)
116 Honey/ (3491)
117 Apitherapy/ (119)
118 (Apitherap* or Honey* or L-Mesitran or MANUKApli or Medihoney* or Melladerm* or Mesitran*).ti,ab. (20130)
119 exp anti-infective agents, local/ (216791)

120 (Antiseptic* or anti-septic* or anti septic* or anti-infective* or anti infective* or antiinfective* or microbicide*).ti,ab. (13997)

121 Acetic Acid/ (9491)

122 (vinegar* or acetic acid*).ti,ab. (38613)

123 Sodium Bicarbonate/ (4377)

124 ((bicarbonate* or baking*) adj2 (sodium* or soda*)).ti,ab. (6339)

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

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

127 Magnesium Sulfate/ (4917)

128 ((Magnesium* or Epsom*) adj2 (sulfate* or sulphate* or salt*)).ti,ab. (5776)

129 or/94-128 (455943)

130 5 and 129 (386)

131 analgesics/ (45865)

132 exp analgesics, non-narcotic/ (312604)

133 analgesics, short-acting/ (9)

134 antipyretics/ (2564)

135 (analgesic* or antipyretic*).ti,ab. (77552)

136 Acetaminophen/ (16915)

137 (paracetamol* or acetaminophen* or Panadol* or perfalgan* or calpol*).ti,ab. (22768)

138 Adrenal Cortex Hormones/ (61432)

139 (Corticosteroid* or corticoid* or Adrenal Cortex Hormone*).ti,ab. (100652)

140 exp Prednisolone/ (49117)

141 (Prednisolone* or Fluprednisolone* or Methylprednisolone* or Deltacortril* or Dilacort* or Pevanti* or Deltastab* or Predsol*).ti,ab. (37586)

142 Anti-Inflammatory Agents, Non-Steroidal/ (63322)

143 nsaid*.ti,ab. (22971)

144 ((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).ti,ab. (36447)

145 Ibuprofen/ (8225)

146 (ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).ti,ab. (12296)

147 or/131-146 (594748)

148 5 and 147 (852)

149 watchful waiting/ (2916)

150 "no intervention*".ti,ab. (7009)

151 (watchful* adj2 wait*).ti,ab. (2338)

152 (wait adj2 see).ti,ab. (1333)

153 (expectant* adj2 manage*).ti,ab. (2956)

154 (active* adj2 surveillance*).ti,ab. (6914)

155 (observing or observe or observes or observation or observations).ti,ab. (739308)

156 or/149-155 (759944)

157 5 and 156 (1464)

158 Inappropriate prescribing/ (2395)

159 ((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab. (29220)

160 ((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. (25563)

161 ((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. (105727)

162 Antibiotic Prophylaxis/ (12742)

163 (prophylaxis* or prophylactic*).ti,ab. (151196)

164 or/158-163 (307194)

165 5 and 164 (1556)

166 anti-infective agents/ or exp anti-bacterial agents/ (691414)

167 (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. (442399)

168 or/166-167 (891389)

169 5 and 168 (2574)

170 68 or 93 or 130 or 148 or 157 or 165 or 169 (6103)

171 limit 170 to yr="2000 -Current" (3987)

172 limit 171 to english language (3468)

173 limit 172 to (letter or historical article or comment or editorial or news) (126)

174 172 not 173 (3342)

175 Meta-Analysis.pt. (94679)

176 Meta-Analysis as Topic/ (16561)

177 Network Meta-Analysis/ (534)

178 Review.pt. (2457838)

179 exp Review Literature as Topic/ (10196)

180 (metaanaly* or metanaly* or (meta adj3 analy*)).ti,ab. (139750)

181 (review* or overview*).ti. (453378)

182 (systematic* adj5 (review* or overview*)).ti,ab. (145976)

183 ((quantitative* or qualitative*) adj5 (review* or overview*)).ti,ab. (9162)

184 ((studies or trial*) adj2 (review* or overview*)).ti,ab. (41784)

185 (integrat* adj3 (research or review* or literature)).ti,ab. (10672)

186 (pool* adj2 (analy* or data)).ti,ab. (26357)

187 (handsearch* or (hand adj3 search*)).ti,ab. (8540)

188 (manual* adj3 search*).ti,ab. (5503)

189 or/175-188 (2744542)

190 174 and 189 (565)

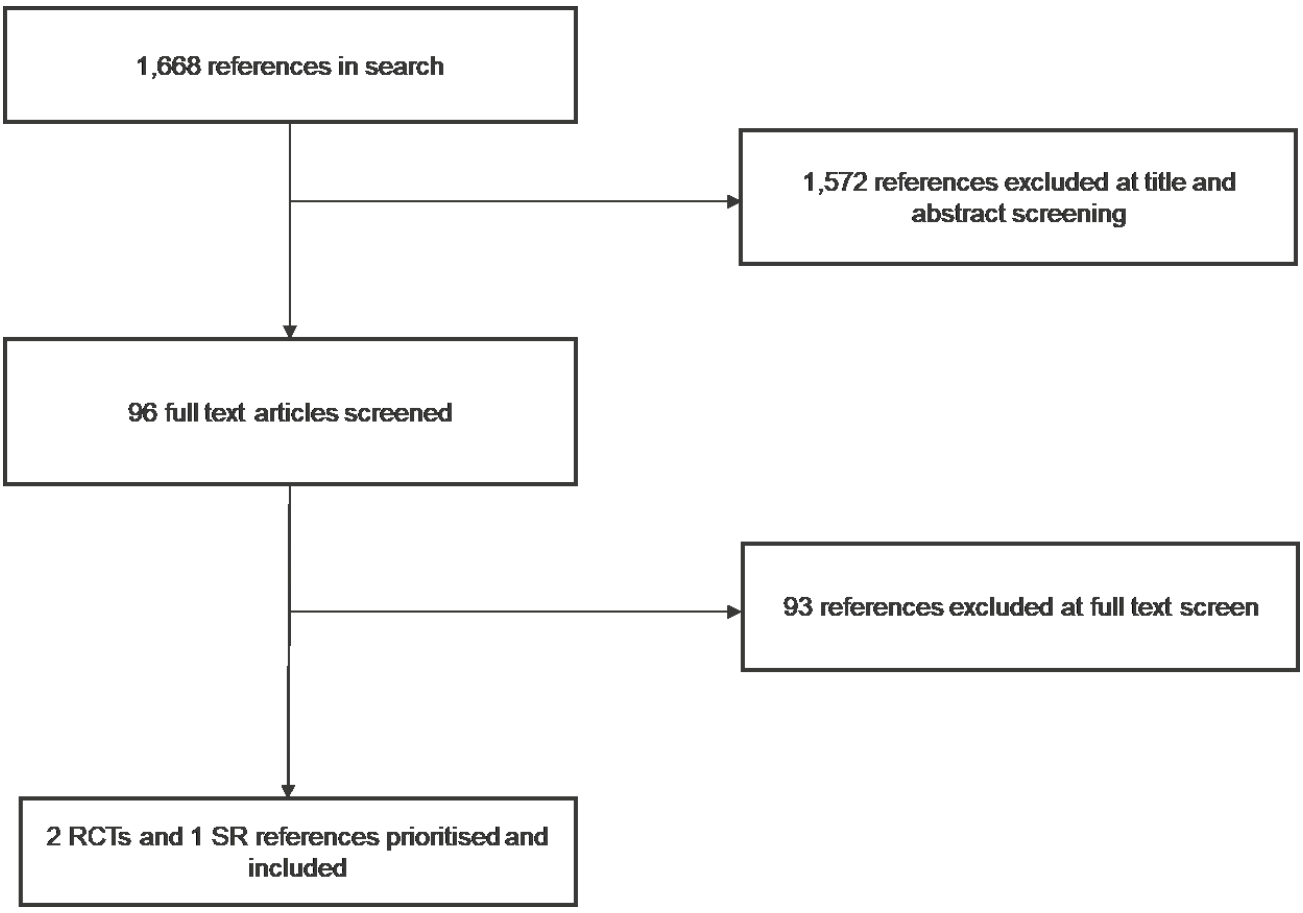
191 68 or 93 or 130 or 148 or 157 or 165 (5102)

192	limit 191 to yr="2000 -Current" (3331)
193	limit 192 to english language (2911)
194	limit 193 to (letter or historical article or comment or editorial or news) (97)
195	193 not 194 (2814)
196	Randomized Controlled Trial.pt. (472058)
197	Controlled Clinical Trial.pt. (92771)
198	Clinical Trial.pt. (513457)
199	exp Clinical Trials as Topic/ (319530)
200	Placebos/ (34152)
201	Random Allocation/ (96642)
202	Double-Blind Method/ (148399)
203	Single-Blind Method/ (25951)
204	Cross-Over Studies/ (44097)
205	((random* or control* or clinical*) adj3 (trial* or stud*)).ti,ab. (1106839)
206	(random* adj3 allocat*).ti,ab. (31949)
207	placebo*.ti,ab. (200046)
208	((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab. (160450)
209	(crossover* or (cross adj over*)).ti,ab. (79905)
210	or/196-209 (1857059)
211	195 and 210 (273)

Key to search operators in above table

/	Medical Subject Heading (MeSH) term
Exp	Explodes the MeSH terms to retrieve narrower terms in the hierarchy
.ti	Searches the title field
.ab	Searches the abstract field
*	Truncation symbol (searches all word endings after the stem)
adj*n*	Adjacency operator to retrieve records containing the terms within a specified number (*n*) of words of each other
?	Wildcard operator – used to retrieve alternate spellings with a single letter variation. For example: *c?t* would retrieve the words *cat*, *cot* and *cut*, and also the acronym *CBT.*

Appendix D: Study flow diagram



Appendix E: Evidence prioritisation

Reference[1]	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
Is prophylactic antibiotic treatment effective for children and adults with an animal and human bite?						
Prophylactic antimicrobial treatments (including oral and topical antibiotics alone or in combination) vs. no antibiotic prophylaxis or placebo						
Mederios et al. 2001	Systematic review	Prophylactic antibiotic for between 5 and 7 days	No antibiotic prophylaxis or placebo	Incidence of infection	Prioritised	Highest quality (most comprehensive) systematic review identified for this comparison
Quinn et al. 2009	RCT	Prophylactic co-amoxiclav for 3 days	Placebo	Incidence of infection	Prioritised	Intervention not included elsewhere
Broder et al. 2002	RCT	Cefalexin/penicillin combination for 5 days	Placebo	Incidence of infection	Prioritised	Intervention not included elsewhere

[1] See appendix F for full references of included studies

Appendix F: Included studies

Broder J, Jerrard D, Olshaker J, et al (2004). Low risk of infection in selected human bites treated without antibiotics. The American Journal of Emergency Medicine 22(1), 10-3

Medeiros I and Saconato H (2001). Antibiotic prophylaxis for mammalian bites. The Cochrane database of systematic reviews (2), CD001738

Quinn JV, McDermott D, Rossi JR, et al (2010.) Randomized controlled trial of prophylactic antibiotics for dog bites with refined cost model. The Western Journal of Emergency Medicine 11(5), 435-41

Appendix G: Quality assessment of included studies

G.1 Antibiotic choice

Table 2: Overall risk of bias/quality assessment – systematic review (ROBIS systematic review checklist)

Study reference	**Medeiros et al. (2001)**
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?	Y – clearly pre-defined objectives and criteria outlined in abstract and main body
1.2 Were the eligibility criteria appropriate for the review question?	Y – criteria restricted by RCT and was aligned with Cochrane methods and process. Focused on dog bites, antibiotic use and incidence of infection
1.3 Were eligibility criteria unambiguous?	N – clearly outlined and focused on animal and human bites with outcomes focused on incidence of infections; clearly outlined inclusion criteria, population and intervention of interest
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	N - criteria restricted by RCT and was aligned with Cochrane methods and process. This is clearly outlined
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	NI – no information was provided regarding restrictions in eligibility criteria based on sources of information
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?	Y – search strategy and protocol clearly outlined (MEDLINE (1966 to 2000), EMBASE (1980 to 2000), LILACS (1988 to 2000) and the Cochrane Controlled Trials Register databases; restriction to RCT and reviews meant unpublished reports not considered
2.2 Were methods additional to database searching used to identify relevant reports?	PY – bibliographic references of identified RCTs, textbooks, review articles and meta-analyses were checked in order to find RCTs not identified by electronic search. A hand search was undertaken to find RCTs presented in Brazilian Infectious Diseases Meetings (1980-1995).

2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	PY – search terms appear limited but relevant
2.4 Were restrictions based on date, publication format, or language appropriate?	PY - MEDLINE (1966 to 2000), EMBASE (1980 to 2000), LILACS (1988 to 2000) and the Cochrane Controlled Trials Register databases; restricted to RCT only; No information regarding restriction by language but all included studies were in English
2.5 Were efforts made to minimise error in selection of studies?	Y - The titles (and abstracts when available) in the MEDLINE, EMBASE, LILACS and hand search of RCTs and reviews were read by the two reviewers. Any article that appeared to meet the inclusion criteria was retrieved. All identified trials were listed and trials excluded from the review were identified with the reasons for exclusion.
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?	Y - An assessment of the quality of the included studies (excluding abstracts) was performed independently by two assessors. The reviewer was not blinded to author, institution and journal of publication of results. The two assessors then reviewed each study together. The Cochrane Collaboration Handbook (Clark and Oxman 2000) and Schulz et al. (Schulz 1995) were used in a standard way to assess risk of bias.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	PY – Types of participants, interventions and outcomes were all reported as were descriptions of studies. Summary of the potential risk of bias were outlined which were sufficient but more study details regarding treatment regimens, specific demographic information would have been useful.
3.3 Were all relevant study results collected for use in the synthesis?	Y – 9 studies were identified but only 8 included in a meta-analysis with dichotomous data extracted (incidence of infection). The study not included in the meta-analysis was due to findings (incidence of infection) not being disaggregated by animal
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y - The two assessors reviewed each study together. The Cochrane Collaboration Handbook (Clark and Oxman 2000) and Schulz et al. (Schulz 1995) were used in a standard way to assess risk of bias.
3.5 Were efforts made to minimise error in risk of bias assessment?	Y - The two assessors then reviewed each study together. The Cochrane Collaboration Handbook (Clark and Oxman 2000) and Schulz et al. (Schulz 1995) were used in a standard way to assess risk of bias.
DOMAIN 4: SYNTHESIS AND FINDINGS Describe synthesis methods:	

4.1 Did the synthesis include all studies that it should?	Y - 9 studies were identified but only 8 included in a meta-analysis with dichotomous data extracted (incidence of infection in prophylactic . The study not included in the meta-analysis was due to findings (incidence of infection) not being disaggregated by animal	
4.2 Were all pre-defined analyses reported or departures explained?	Y – the study sought to assess the effect of antibiotic prophylaxis vs placebo for the treatment of mammalian bites. The primary outcome was incidence of infection and 3 meta-analysis were undertaken that considered where data allowed: type of mammal, type of bite and location of bite; This is a Cochrane review and follows its methods and process	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y – all RCT, dichotomous outcomes, random-effects meta-analysis to account for differences across studies for example in antibiotic treatments and placebo could sometimes involve wound treatment	
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	N – I^2 for some comparisons was over 40% indicating high heterogeneity. Number of participants in each study was low. The quality of the included RCT's would be categorised as low. Intention to treat analysis was performed. Heterogeneity between RCTs was tested using a chi-square test (with a p-value of less than 0.1 indicating significant heterogeneity) and by inspecting the graphical presentation. Odds ratio with respective confidence intervals (CI) using random effects model was reported. When appropriate, the number of patients that it was necessary to treat to prevent one case of bacterial infection was calculated (NNT = number needed to treat).	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y – although a funnel plot was not outlined in the review, the study refers to a funnel plot being done which according to the author did not demonstrate any apparent asymmetry thus low publication bias. Sensitivity analyses were undertaken, which consisted of repeating the analysis taking account of study quality, excluding studies with poor quality and repeating the analysis using different statistical models (fixed and random effects models)	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	PN – The authors flag that allocation concealment was adequate in only 1/8 studies, randomisation was appropriate in 2/8 studies with no descriptions of randomisation outlined in 6/8 studies. It Is unclear in the methods of the review how this is accounted for.	
PHASE 3: JUDGING RISK OF BIAS	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria	Low	All aspects answered as yes apart from 1.5 where not enough information was available, but this is not thought to raise any concerns

2. Concerns regarding methods used to identify and/or select studies	Low	2.1 to 2.5 were all rated Y or PY so no potential areas of bias were identified
3. Concerns regarding methods used to collect data and appraise studies	Low	Risk of bias was assessed using appropriate criteria, data extraction and risk of bias assessment involved two reviewers, and relevant study characteristics and results were extracted.
4. Concerns regarding the synthesis and findings	High	Absence of narrative regarding how issues of concealment and the absence of information regarding randomisation in the majority of included studies is a concern and would indicate that bias was not fully considered in subsequent analysis; Included RCT's were of poor methodological quality
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?	PY – no issues raised across domains 1-3, and all domains of 4 apart from 4.6. However, the authors outline the limitations of the findings in discussion and conclusions section	
B. Was the relevance of identified studies to the review's research question appropriately considered?	Y – The review utilised Cochrane methods and process, undertook adequate searching and appraisal processes. The studies identified were of low quality but applicable to the review research question	
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y - the authors flag the limitations of the findings outlining the high heterogeneity in the meta-analysis	
Risk of bias in the review RISK: Rationale for risk:	High – Only one study in the review was adjudged to have adequate allocation concealment; Only two studies were adjudged to have appropriate methods of randomisation generation; None of the included studies outlined their method of randomisation; Three studies did not report the extent of loss to follow-up; Three studies had losses to follow-up >10%; All but one study was adjudged to be at either unclear (n=6) or high (n=1) risk of bias.	

G.2 Antibiotic choice

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

Study reference	Quinn et al 2009	Broder et al 2002
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 -** a computerized randomization code identified, Three-day courses of blinded medication was prepared and no differences were identified to indicate problems with randomization	**Some concerns** – no information on randomization; concealment via pre-packaged both placebo and antibiotic in individual containers; no statistically significant differences between groups
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** – Blinding was outlined; details regarding analysis used to estimate the effect of assignment to intervention appears to be a naïve per protocol	**Some concerns** – Blinding outlined; 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	**Low** – blinding clear; 3 participants withdrew (reasons not outlined).	**Low –** blinding and concealment outlined but minimal detail; 2 participants lost to follow-up.
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** - incidence of infection based on patient signs and symptoms; unclear if the same blinded physician was used but blinding reported;	**Low -** incidence of infection based on patient signs and symptoms assessed by same blinded examiner
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	**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	**Some concerns**	**Some concerns**
Optional: What is the overall predicted direction of bias due to selection of the reported result?	**Unpredictable**	**Unpredictable**

Appendix H: GRADE profiles

H.1 Antibiotic prophylaxis versus no antibiotic prophylaxis or placebo

H.1.1 Dog, cat and human bites

Table 4: GRADE profile – Antibiotic prophylaxis versus no antibiotic prophylaxis or placebo for the treatment of human and animal bites

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Control	Relative (95% CI)	Absolute		
Prophylactic antibiotics vs placebo (signs of infection from dog, cat and human bites[4])												
10[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	10/374 (2.7%)	29/367 (8.0%)	NICE analysis: RR 0.46 (0.20 to 1.07)	43 fewer per 1000 (from 63 fewer to 6 more)	⊕⊕OO LOW	CRITICAL

[1] Medeiros et al. 2001, Broder et al. 2002 and Quinn et al. 2009
[2] Downgraded 1 level – Lack of adequate allocation concealment in some studies; lack of appropriate methods of randomisation generation in some studies; Extent of loss to follow-up not reported in all studies with some studies having losses to follow-up >10%; 7/8 studies assessed as being at unclear (n=6) or high (n=1) risk of bias (Medeiros et al. 2001); the study lacked details to confirm the randomisation, blinding and concealment process (Broder et al. 2004); A lack of detail with which to assess if an appropriate analysis was used to estimate the effect of assignment to intervention; unclear if the same blinded physician was used to measure outcomes across intervention groups (Quinn et al. 2010)
[3] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction the effect estimate is consistent with appreciable benefit
[4] Signs of infection were not specified within the included RCTs included in Medeiros et al (2001) but types of outcomes measures that could be considered included: Proven bacterial infection: clinical signs (temperature, induration, erythema, swelling, pain, warmth, pus, odour, adenopathy, lymphangitis, cellulitis) plus positive microbiological cultures (for aerobics and anaerobic) at the site of bite; Presumptive bacterial infection: clinical signs of infection at the site of bite with negative culture (or culture not obtained). Broder et al (2002) included local erythema, warmth, tenderness, lymphangitis, induration, purulent discharge, or fever and Quinn et al (2009) included redness or discharge as signs of infection.

H.1.2 Dog bites

Table 5: GRADE profile – Antibiotic prophylaxis versus no antibiotic prophylaxis or placebo for the treatment of dog bites

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotics**	**Control**	**Relative (95% CI)**	**Absolute**		
Prophylactic antibiotics vs placebo (signs of infection from dog bites[4])												
7[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/273 (3.7%)	17/284 (6.0%)	NICE analysis: RR 0.64, (0.28 to 1.45)	22 fewer per 1000 (from 43 fewer to 27 more)	⊕OOO VERY LOW	CRITICAL

[1] Medeiros et al. 2001 and Quinn et al. 2009
[2] Downgraded 1 level – Lack of adequate allocation concealment in some studies; lack of appropriate methods of randomisation generation in some studies; extent of loss to follow-up not reported in all studies with some studies having losses to follow-up >10%; 5/6 studies assessed as being at unclear (n=4) or high (n=1) risk of bias (Medeiros et al. 2001); The study lacked details to confirm the randomisation, blinding and concealment process (Broder et al. 2004); A lack of detail with which to assess if an appropriate analysis was used to estimate the effect of assignment to intervention; unclear if the same blinded physician was used to measure outcomes across intervention groups (Quinn et al. 2010)
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm
[4] Signs of infection were not specified within the included RCTs included in Medeiros et al (2001) but types of outcomes measures that could be considered included: Proven bacterial infection: clinical signs (temperature, induration, erythema, swelling, pain, warmth, pus, odour, adenopathy, lymphangitis, cellulitis) plus positive microbiological cultures (for aerobics and anaerobic) at the site of bite; Presumptive bacterial infection: clinical signs of infection at the site of bite with negative culture (or culture not obtained). Broder et al (2002) included local erythema, warmth, tenderness, lymphangitis, induration, purulent discharge, or fever as signs of infection.

H.1.3 Cat bites

Table 6: GRADE profile – Antibiotic prophylaxis versus placebo for the treatment of cat bites

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotics**	**Control**	**Relative (95% CI)**	**Absolute**		
Prophylactic antibiotics (Oxacillin) vs placebo (signs of infection from cat bites[4])												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/5 (0%)	4/6 (66.7%)	NICE analysis: RR 0.13 (0.01 to 1.95)	580 fewer per 1000 (from 660 fewer to 633 more)	⊕OOO VERY LOW	CRITICAL

[1] Medeiros et al. (2001)
[2] Downgraded 1 level – method of randomisation unspecified; study assessed as being at unclear risk of bias
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm

[4] Signs of infection were not specified within the included RCTs included in Medeiros et al (2001) but types of outcomes measures that could be considered included: Proven bacterial infection: clinical signs (temperature, induration, erythema, swelling, pain, warmth, pus, odour, adenopathy, lymphangitis, cellulitis) plus positive microbiological cultures (for aerobics and anaerobic) at the site of bite; Presumptive bacterial infection: clinical signs of infection at the site of bite with negative culture (or culture not obtained).

H.1.4 Human bites

Table 7: GRADE profile –Antibiotic prophylaxis versus placebo for the treatment of human bites

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Control	Relative (95% CI)	Absolute		
Prophylactic antibiotics vs placebo (signs of infection from all human bites[6])												
2[1]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	0/96 (0%)	8/77 (10.4%)	NICE analysis: RR 0.09 (0.01 to 0.92)	95 fewer per 1000 (from 8 fewer to 103 fewer)	⊕⊕OO LOW	CRITICAL
Prophylactic antibiotics vs placebo (signs of infection from high-risk human bites[6])												
1[2]	Randomised trial	serious[5]	no serious inconsistency	no serious indirectness	no serious indirectness	none	0/33 (0%)	7/15 (46.7%)	NICE analysis: RR 0.03 (0.00 to 0.52)	453 fewer per 1000 (from 224 fewer to 467 fewer)	⊕⊕⊕O MODERATE	CRITICAL

[1] Medeiros et al. (2001) and Broder et al. (2004)
[2] Medeiros et al. (2001)
[3] Downgraded 1 level - study assessed as being at unclear risk of bias with the method of randomisation unspecified (Medeiros et al. 2001); the study lacked details to confirm the randomisation, blinding and concealment process (Broder et al. 2004)
[4] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction the effect estimate is consistent with appreciable benefit
[5] Downgraded 1 level - study assessed as being at unclear risk of bias with the method of randomisation unspecified (Medeiros et al. 2001)
[6] Signs of infection were not specified within the included RCTs included in Medeiros et al (2001) but types of outcomes measures that could be considered included: Proven bacterial infection: clinical signs (temperature, induration, erythema, swelling, pain, warmth, pus, odour, adenopathy, lymphangitis, cellulitis) plus positive microbiological cultures (for aerobics and anaerobic) at the site of bite; Presumptive bacterial infection: clinical signs of infection at the site of bite with negative culture (or culture not obtained). Broder et al (2002) included local erythema, warmth, tenderness, lymphangitis, induration, purulent discharge, or fever as signs of infection.

H.1.5 Type of wound

Table 8: GRADE profile - Antibiotic prophylaxis versus placebo for the treatment of human and animal bites by wound type

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Control	Relative (95% CI)	Absolute		
Prophylactic antibiotics vs placebo (puncture wound - incidence of infection[4])												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/14 (7.1%)	5/16 (31.3%)	NICE analysis: RR 0.38 (0.03 to 4.13)	194 fewer per 1000 (from 303 fewer to 978 more)	⊕OOO VERY LOW	CRITICAL
Prophylactic antibiotics vs placebo (laceration wound - incidence of infection[4])												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/63 (3.2%)	4/66 (6.1%)	NICE analysis: RR 0.79 (0.06 to 11.03)	13 fewer per 1000 (from 57 fewer to 608 more)	⊕OOO VERY LOW	CRITICAL
Prophylactic antibiotics vs placebo (avulsions wound - incidence of infection[4])												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/41 (4.9%)	1/30 (3.3%)	NICE analysis: RR 1.06 (0.12 to 9.24)	2 more per 1000 (from 29 fewer to 275 more)	⊕OOO VERY LOW	CRITICAL

[1] Medeiros et al. (2001)
[2] Downgraded 1 level - all studies assessed as being at unclear risk of bias rationale included unclear method of randomisation; no other details were provided
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm
[4] Signs of infection were not specified within the included RCTs included in Medeiros et al (2001) but types of outcomes measures that could be considered included: Proven bacterial infection: clinical signs (temperature, induration, erythema, swelling, pain, warmth, pus, odour, adenopathy, lymphangitis, cellulitis) plus positive microbiological cultures (for aerobics and anaerobic) at the site of bite; Presumptive bacterial infection: clinical signs of infection at the site of bite with negative culture (or culture not obtained).

H.1.6 Location of wound

Table 9: GRADE profile - Antibiotic prophylaxis versus placebo for the treatment of human and animal bites by wound site

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Control	Relative (95% CI)	Absolute		

Prophylactic antibiotics vs placebo (trunk wound - incidence of infection[7])												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/15 (6.7%)	0/17 (0%)	NICE analysis: RR 1.50 (0.10 to 22.62)	not estimable	⊕OOO VERY LOW	CRITICAL
Prophylactic antibiotics vs placebo (head/neck wound - incidence of infection[7])												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/41 (0%)	1/41 (2.4%)	NICE analysis: RR 0.32 (0.01 to 7.48)	17 fewer per 1000 (from 24 fewer to 158 more)	⊕OOO VERY LOW	CRITICAL
Prophylactic antibiotics vs placebo (hands wound - incidence of infection[7])												
3[1]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	1/61 (1.6%)	12/43 (27.9%)	NICE analysis: RR 0.16 (0.02 to 1.17)	234 fewer per 1000 (from 273 fewer to 47 more)	⊕⊕OO LOW	CRITICAL
Prophylactic antibiotics vs placebo (arm wound - incidence of infection[7])												
1[1]	randomised trial	very serious[6]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/2 (0%)	0/3 (0%)	-	-	⊕OOO VERY LOW	CRITICAL

[1] Medeiros et al (2001)
[2] Downgraded 1 level - all studies were assessed as being at unclear risk of bias with methods of randomisation outlined as unclear and no further details provided in the review
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction or relative risk increase, the effect estimate is consistent with appreciable benefit and appreciable harm
[4] Downgraded 1 level - all studies were assessed as being at unclear risk of bias with methods of randomisation outlined as unclear and no further details provided in the review
[5] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction the effect estimate is consistent with appreciable benefit
[6] Downgraded 2 levels - low sample size and zero arm wound events; effect could not be calculated; study assessed as being at unclear risk of bias
[7] Signs of infection were not specified within the included RCTs included in Medeiros et al (2001) but types of outcomes measures that could be considered included: Proven bacterial infection: clinical signs (temperature, induration, erythema, swelling, pain, warmth, pus, odour, adenopathy, lymphangitis, cellulitis) plus positive microbiological cultures (for aerobics and anaerobic) at the site of bite; Presumptive bacterial infection: clinical signs of infection at the site of bite with negative culture (or culture not obtained).

H.2 Antibiotic compared with antibiotic in adults, young people and children

No systematic reviews or randomised controlled trials met the inclusion criteria

H.3 Antibiotic dose in adults, young people and children

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.4 Antibiotic dose frequency in adults, young people and children

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.5 Antibiotic course length in adults, young people and children

No systematic reviews or randomised controlled trials met the inclusion criteria.

Appendix I: Studies not prioritised

No studies were deprioritised

Appendix J: Excluded studies

Study reference	Reason for exclusion
Abuabara Allan (2006) A review of facial injuries due to dog bites. Medicina oral, and patologia oral y cirugia bucal 11(4), E348-50	Excluded: not a systematic review or a randomised controlled trial
Abu-Zidan F M, Abdel-Kader S, El Husseini , and R (2014) Common carotid artery injury caused by a camel bite: Case report and systematic review of the literature. Ulusal Travma ve Acil Cerrahi Dergisi 20(1), 59-62	Excluded: not a systematic review or a randomised controlled trial
Amate Blanco, J M, Bouza Álvarez, C , Conde Espejo, P , Chippaux J P, De Haro , L , Del Pino Luengo, M , Estefanía Díaz, M E, García Ubbelohde, W , García Willis, C , Lisa Catón, V , Martín Sierra, M C, Méndez García, J L, Nogué Xarau, S , Oteo J A, Palomar A M, Saz Parkinson, and Z (2012) 1st Expert Panel on viper venomous bite in Spain. : ,	Excluded: study not available in English
Avila-Agüero M L, París M M, Hu S, Peterson P K, Gutiérrez J M, Lomonte B, and Faingezicht I (2001) Systemic cytokine response in children bitten by snakes in Costa Rica. Pediatric emergency care 17(6), 425-429	Excluded: not a systematic review or a randomised controlled trial
Baculik T, Eckburg P B, Friedland H D, Llorens L, Schraa C C, and Jandourek A (2011) CANVAS 1 and 2: analysis of clinical response at Day 3 from 2 phase III trials of ceftaroline fosamil vs vancomycin plus aztreonam in the treatment of complicated skin and skin structure infections. Pharmacotherapy 31(10), 351e	Excluded: not a systematic review or a randomised controlled trial
Ball V, and Younggren B N (2007) Emergency Management of Difficult Wounds: Part I. Emergency Medicine Clinics of North America 25(1), 101-121	Excluded: not a systematic review or a randomised controlled trial
Booth A (2001) Topic: Antibiotics for dog bites. Journal of Clinical Excellence 3(1), 42-43	Excluded: not a systematic review or a randomised controlled trial
Booth A (2001) Topic: Antibiotics for dog bites. Journal of Clinical Excellence 3(1), 42-43	Excluded: duplicate study
Boyd J J, Agazzi G, Svajda D, Morgan A J, Ferrandis S, and Norris R L (2007) Venomous snakebite in mountainous terrain: Prevention and management. Wilderness and Environmental Medicine 18(3), 190-202	Excluded: not a systematic review or a randomised controlled trial
Broder J, Jerrard D, Olshaker J, and Witting M (2004) Article 1 - Lowrisk of infection in selected human bites treated without antibiotics. Medecine et Maladies Infectieuses 34(6), 273-277	Excluded: duplicate study
Brook Itzhak (2003) Microbiology and management of human and animal bite wound infections. Primary care 30(1), 25-v	Excluded: not a systematic review or a randomised controlled trial
Bula-Rudas Fernando J, and Olcott Jessica L (2018) Human and Animal Bites. Pediatrics in review 39(10), 490-500	Excluded: not a systematic review or a randomised controlled trial
Butler T (2015) Capnocytophaga canimorsus: an emerging cause of sepsis, meningitis, and post-splenectomy infection after dog bites. European journal of clinical microbiology & infectious	Excluded: not a systematic review or a randomised controlled trial

Study reference	Reason for exclusion
diseases : official publication of the European Society of Clinical Microbiology 34(7), 1271-80	
Cardall T Y, and Rosen P (2003) Grizzly bear attack. Journal of Emergency Medicine 24(3), 331-333	Excluded: not a systematic review or a randomised controlled trial
Carneiro P M, and Nyawawa E T (2003) Topical phenytoin versus EUSOL in the treatment of non-malignant chronic leg ulcers. East african medical journal 80(3), 124-129	Excluded: outcomes not relevant
Chaudhry Mehmood A, Macnamara Aidan F, and Clark Shane (2004) Is the management of dog bite wounds evidence based? A postal survey and review of the literature. European journal of emergency medicine : official journal of the European Society for Emergency Medicine 11(6), 313-7	Excluded: not a systematic review or a randomised controlled trial
Cheng H T, Hsu Y C, and Wu C I (2014) Does primary closure for dog bite wounds increase the incidence of wound infection? A meta-analysis of randomized controlled trials. : , 1448-1450	Excluded: intervention not relevant
Cheung Kevin, Hatchell Alexandra, and Thoma Achilleas (2013) Approach to traumatic hand injuries for primary care physicians. Canadian family physician Medecin de famille canadien 59(6), 614-8	Excluded: not a systematic review or a randomised controlled trial
Chhabra Shruti, Chhabra Naveen, and Gaba Shivani (2015) Maxillofacial injuries due to animal bites. Journal of maxillofacial and oral surgery 14(2), 142-53	Excluded: not a systematic review or a randomised controlled trial
Correira Kristine (2003) Managing dog, cat, and human bite wounds. JAAPA : official journal of the American Academy of Physician Assistants 16(4), 28-37	Excluded: study could not be retrieved
Dendle Claire, and Looke David (2008) Review article: Animal bites: an update for management with a focus on infections. Emergency medicine Australasia : EMA 20(6), 458-67	Excluded: not a systematic review or a randomised controlled trial
Doshi Deepak, Foex Bernard A, and Nataly Yogesh (2015) BET 2: role of vinegar in Irukandji syndrome. Emergency medicine journal : EMJ 32(12), 970-1	Excluded: not a systematic review or a randomised controlled trial
Doshi Deepak, Foex Bernard A, and Nataly Yogesh (2015) Towards evidence-based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 1: role of vinegar in Irukandji syndrome. Emergency medicine journal : EMJ 32(3), 250-1	Excluded: duplicate study
Edens Mary Ann, Michel Jose A, and Jones Nathaniel (2016) Mammalian Bites In The Emergency Department: Recommendations For Wound Closure, Antibiotics, And Postexposure Prophylaxis. Emergency medicine practice 18(4), 1-20	Excluded: study could not be retrieved
Ellis Robert, and Ellis Carrie (2014) Dog and cat bites. American family physician 90(4), 239-43	Excluded: not a systematic review or a randomised controlled trial
Erickson Benjamin P, Feng Paula W, Liao Sophie D, Modi Yasha S, Ko Audrey C, and Lee Wendy W (2018) Dog bite injuries of the eye and ocular adnexa. Orbit (Amsterdam, and Netherlands) , 1-8	Excluded: not a systematic review or a randomised controlled trial

Study reference	Reason for exclusion
Esposito S, Picciolli I, Semino M, and Principi N (2013) Dog and cat bite-associated infections in children. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 32(8), 971-6	Excluded: not a systematic review or a randomised controlled trial
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 56(5), 2231-2236	Excluded: study population not bitten by animal or human
Glaser C, Lewis P, and Wong S (2000) Pet-, animal-, and vector-borne infections. Pediatrics in review 21(7), 219-32	Excluded: not a systematic review or a randomised controlled trial
Gold B S, Dart R C, and Barish R A (2002) Current concepts: Bites of venomous snakes. New England Journal of Medicine 347(5), 347-356	Excluded: not a systematic review or a randomised controlled trial
Gouin S, and Patel H (2001) Office management of minor wounds. Canadian Family Physician 47(APR.), 769-774	Excluded: not a systematic review or a randomised controlled trial
Harrison Mark (2009) A 4-year review of human bite injuries presenting to emergency medicine and proposed evidence-based guidelines. Injury 40(8), 826-30	Excluded: not a systematic review or a randomised controlled trial
Henton J, and Jain A (2012) Cochrane corner: antibiotic prophylaxis for mammalian bites (intervention review). The Journal of hand surgery, and European volume 37(8), 804-6	Excluded: not a systematic review or a randomised controlled trial
Hopkins Teri L, Daley Mitchell J, Rose Dusten T, Jaso Theresa C, and Brown Carlos V. R (2016) Presumptive antibiotic therapy for civilian trauma injuries. The journal of trauma and acute care surgery 81(4), 765-74	Excluded: not a systematic review or a randomised controlled trial
Iqbal Tanzeem (2008) Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 1. Antibiotics in cat bites. Emergency medicine journal : EMJ 25(10), 686-7	Excluded: not a systematic review or a randomised controlled trial
Isci E T, and Ritter E (2018) On the complexity of shark bite wounds: From associated bacteria to trauma management and wound repair. Journal of Trauma and Acute Care Surgery 85(2), 398-405	Excluded: not a systematic review or a randomised controlled trial
Israel Jacqueline S, McCarthy James E, Rose Katherine R, and Rao Venkat K (2017) Watch Out for Wild Animals: A Systematic Review of Upper Extremity Injuries Caused by Uncommon Species. Plastic and reconstructive surgery 140(5), 1008-1022	Excluded: not a systematic review or a randomised controlled trial
Jorge M T, Malaque C, Ribeiro L A, Fan H W, Cardoso J L, Nishioka S A, Sano-Martins I S, França F O, Kamiguti A S, Theakston R D, and et al (2004) Failure of chloramphenicol prophylaxis to reduce the frequency of abscess formation as a complication of envenoming by Bothrops snakes in Brazil: a double-blind randomized controlled trial. Transactions of the royal society of tropical medicine and hygiene 98(9), 529-534	Excluded: focused on the use of antibiotics to resolve complications from envenoming
Kennedy Stephen A, Stoll Laura E, and Lauder Alexander S (2015) Human and other mammalian bite injuries of the hand:	Excluded: not a systematic review or a randomised controlled trial

Study reference	Reason for exclusion
evaluation and management. The Journal of the American Academy of Orthopaedic Surgeons 23(1), 47-57	
Kristinsson George (2007) Pasteurella multocida infections. Pediatrics in review 28(12), 472-3	Excluded: not a systematic review or a randomised controlled trial
Kularatne S A. M, Kumarasiri P V. R, Pushpakumara S K. C, Dissanayaka W P, Ariyasena H, Gawarammana I B, and Senanayake N (2005) Routine antibiotic therapy in the management of the local inflammatory swelling in venomous snakebites: results of a placebo-controlled study. The Ceylon medical journal 50(4), 151-5	Excluded: outcomes not relevant
Ladhani Shamez, and Garbash Mehdi (2005) Staphylococcal skin infections in children: rational drug therapy recommendations. Paediatric drugs 7(2), 77-102	Excluded: population not relevant
Li Li, McGee Richard G, Isbister Geoff, and Webster Angela C (2013) Interventions for the symptoms and signs resulting from jellyfish stings. The Cochrane database of systematic reviews (12), CD009688	Excluded: intervention not relevant
Looke David, and Dendle Claire (2010) Bites (Mammalian). BMJ clinical evidence 2010,	Excluded: not a systematic review or a randomised controlled trial
Marques de Medeiros, Iara , and Saconato Humberto (2002) Mammalian bites. Clinical evidence (7), 692-7	Excluded: not a systematic review or a randomised controlled trial
Marques de Medeiros, Iara , and Saconato Humberto (2002) Mammalian bites. Clinical evidence (7), 692-7	Excluded: duplicate study
May A K, Stafford R E, Bulger E M, Heffernan D, Guillamondegui O, Bochicchio G, and Eachempati S R (2009) Treatment of complicated skin and soft tissue infections. Surgical Infections 10(5), 467-499	Excluded: not a systematic review or a randomised controlled trial
McDermitt B A, Romanchak N L, and Ponte C D (2002) The management of dog bites. Journal of Pharmacy Technology 18(2), 63-69	Excluded: not a systematic review or a randomised controlled trial
Montgomery Louise, Seys Jan, and Mees Jan (2016) To Pee, or Not to Pee: A Review on Envenomation and Treatment in European Jellyfish Species. Marine drugs 14(7),	Excluded: intervention not relevant
Morgan M (2003) The bacteriology and clinical aspects of bites. CPD Infection 4(2), 44-48	Excluded: study could not be retrieved
Morgan M (2003) The bacteriology and clinical aspects of bites. CPD Infection 4(2), 44-48	Excluded: duplicate study
Morgan M (2005) Hospital management of animal and human bites. Journal of Hospital Infection 61(1), 1-10	Excluded: not a systematic review or a randomised controlled trial
Morgan M, and Palmer J (2007) Dog bites. British Medical Journal 334(7590), 413-417	Excluded: not a systematic review or a randomised controlled trial
Morgan Marina, and Palmer John (2007) Dog bites. BMJ (Clinical research ed.) 334(7590), 413-7	Excluded: duplicate study

Study reference	Reason for exclusion
Muhi S, and Denholm J (2017) Human and animal bites Managing and preventing infection. Medicine Today 18(11), 30-40	Excluded: not a systematic review or a randomised controlled trial
Noonburg Greer E (2005) Management of extremity trauma and related infections occurring in the aquatic environment. The Journal of the American Academy of Orthopaedic Surgeons 13(4), 243-53	Excluded: not a systematic review or a randomised controlled trial
Norton Cormac (2008) Animal and human bites. Emergency nurse : the journal of the RCN Accident and Emergency Nursing Association 16(6), 26-9	Excluded: not a systematic review or a randomised controlled trial
Nuchprayoon I, Pongpan C, and Sripaiboonkij N (2008) The role of prednisolone in reducing limb oedema in children bitten by green pit vipers: a randomized, controlled trial. Annals of tropical medicine and parasitology 102(7), 643-9	Excluded: intervention not relevant
O'Riordan William, Mehra Purvi, Manos Paul, Kingsley Jeff, Lawrence Laura, and Cammarata Sue (2015) A randomized phase 2 study comparing two doses of delafloxacin with tigecycline in adults with complicated skin and skin-structure infections. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 30, 67-73	Excluded: outcomes not relevant
Parker-Cote Jennifer, and Meggs William J (2018) First Aid and Pre-Hospital Management of Venomous Snakebites. Tropical medicine and infectious disease 3(2),	Excluded: intervention not relevant
Patton Carol M (2003) Animal-inflicted hand wounds. Treat early and aggressively. Advance for nurse practitioners 11(7), 57-62	Excluded: not a systematic review or a randomised controlled trial
Pennie Ross A, Szakacs Thomas A, Smaill Fiona M, Smieja Marek, Yamamura Deborah, McTaggart Barrie, and McCallum Andrew (2004) Short report: Ceftriaxone for cat and dog bites. Simple outpatient treatment. Canadian family physician Medecin de famille canadien 50, 577-9	Excluded: not a systematic review or a randomised controlled trial
Prestwich Heather, and Jenner Rachel (2007) Best evidence topic report. Treatment of jellyfish stings in UK coastal waters: vinegar or sodium bicarbonate?. Emergency medicine journal : EMJ 24(9), 664	Excluded: intervention not relevant
Presutti J R (2001) Prevention and treatment of dog bites. American Family Physician 63(8), 1567-1572	Excluded: not a systematic review or a randomised controlled trial
Riesland Nicholas J, and Wilde Henry (2015) Expert Review of Evidence Bases for Managing Monkey Bites in Travelers. Journal of travel medicine 22(4), 259-62	Excluded: not a systematic review or a randomised controlled trial
Rittner Alma-Victoria, Fitzpatrick Kevin, and Corfield Alasdair (2005) Best evidence topic report. Are antibiotics indicated following human bites?. Emergency medicine journal : EMJ 22(9), 654	Excluded: not a systematic review or a randomised controlled trial
Riviello R, and Lavelle K G (2005) Human and animal bites: Acute care and follow-up. Consultant 45(10), 1091-1100	Excluded: not a systematic review or a randomised controlled trial

Study reference	Reason for exclusion
Roberts S A, and Lang S D. R (2000) Skin and soft tissue infections. New Zealand Medical Journal 113(1109), 164-167	Excluded: not a systematic review or a randomised controlled trial
Roberts S A, and Lang S D. R (2000) Skin and soft tissue infections. New Zealand Medical Journal 113(1109), 164-167	Excluded: duplicate study
Rodriguez A J, Barbella R, and Castaneda L (2000) Anaerobic dog bite wound infection. Annals of the New York Academy of Sciences 916, 665-7	Excluded: not a systematic review or a randomised controlled trial
Sachett JAG, da Silva IM, Alves EC, et al (2017). Poor efficacy of preemptive amoxicillin clavulanate for preventing secondary infection from Bothrops snakebites in the Brazilian Amazon: a randomized controlled clinical trial. PLoS neglected tropical diseases 11(7), e0005745	Excluded: study population – snake bites from a snake endemic to South America
Schadel-Hopfner M, Windolf J, Antes G, Sauerland S, and Diener M K (2008) Evidence-bdased hand surgery: The role of cochrane reviews. Journal of Hand Surgery: European Volume 33(2), 110-117	Excluded: not a systematic review or a randomised controlled trial
Shirtliff M E, and Mader J T (2002) Acute septic arthritis. Clinical Microbiology Reviews 15(4), 527-544	Excluded: population not relevant
Shoji Kristin, Cavanaugh Zachary, and Rodner Craig M (2013) Acute fight bite. The Journal of hand surgery 38(8), 1612-4	Excluded: not a systematic review or a randomised controlled trial
Singer Adam J, and Dagum Alexander B (2008) Current management of acute cutaneous wounds. The New England journal of medicine 359(10), 1037-46	Excluded: not a systematic review or a randomised controlled trial
Smith H R, Hartman H, Loveridge J, and Gunnarsson R (2016) Predicting serious complications and high cost of treatment of tooth-knuckle injuries: a systematic literature review. European journal of trauma and emergency surgery : official publication of the European Trauma Society 42(6), 701-710	Excluded: outcomes not relevant
Spelman D, Buttery J, Daley A, Isaacs D, Jennens I, Kakakios A, Lawrence R, Roberts S, Torda A, Watson D A. R, Woolley I, Anderson T, and Street A (2008) Guidelines for the prevention of sepsis in asplenic and hyposplenic patients. Internal Medicine Journal 38(5), 349-356	Excluded: population not relevant
Stefanopoulos P K, and Tarantzopoulou A D (2005) Facial bite wounds: management update. International journal of oral and maxillofacial surgery 34(5), 464-72	Excluded: not a systematic review or a randomised controlled trial
Stefanopoulos Panagiotis K (2009) Management of facial bite wounds. Oral and maxillofacial surgery clinics of North America 21(2), 247-vii	Excluded: not a systematic review or a randomised controlled trial
Stefanopoulos Panagiotis K, and Tarantzopoulou Andromache D (2009) Management of facial bite wounds. Dental clinics of North America 53(4), 691-vi	Excluded: duplicate study
Stefanopoulos Panayotis, Karabouta Zacharoula, Bisbinas Ilias, Georgiannos Dimitrios, and Karabouta Irene (2004) Animal and human bites: evaluation and management. Acta orthopaedica Belgica 70(1), 1-10	Excluded: not a systematic review or a randomised controlled trial

Study reference	Reason for exclusion
Stevens D L (2009) Treatments for skin and soft-tissue and surgical site infections due to MDR Gram-positive bacteria. Journal of Infection 59(SUPPL. 1), S32-S39	Excluded: not a systematic review or a randomised controlled trial
Stevens D L, Bisno A L, Chambers H F, Dellinger E P, Goldstein E J. C, Gorbach S L, Hirschmann J V, Kaplan S L, Montoya J G, and Wade J C (2014) Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clinical Infectious Diseases 59(2), e10-e52	Excluded: outcomes not relevant
Stevens D L, Bisno A L, Chambers H F, Everett E D, Dellinger P, Goldstein E J. C, Gorbach S L, Hirschmann J V, Kaplan E L, Montoya J G, and Wade J C (2005) Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clinical Infectious Diseases 41(10), 1373-1406	Excluded: not a systematic review or a randomised controlled trial
Taplitz Randy A (2004) Managing bite wounds. Currently recommended antibiotics for treatment and prophylaxis. Postgraduate medicine 116(2), 49-59	Excluded: not a systematic review or a randomised controlled trial
Turina Matthias, and Cheadle William G (2005) Clinical challenges and unmet needs in the management of complicated skin and skin structure, and soft tissue infections. Surgical infections 6 Suppl 2, S-36	Excluded: not a systematic review or a randomised controlled trial
Turner Troy W. S (2004) Evidence-based emergency medicine/systematic review abstract. Do mammalian bites require antibiotic prophylaxis?. Annals of emergency medicine 44(3), 274-6	Excluded: not a systematic review or a randomised controlled trial
Villani Nadine M (2006) Treating dog and cat bites. Advance for nurse practitioners 14(7), 44-5	Excluded: not a systematic review or a randomised controlled trial
Vondra M S, and Myers J P (2011) Pasteurella multocida bacteremia: Report of 12 cases in the 21st Century and comprehensive review of the adult literature. Infectious Diseases in Clinical Practice 19(3), 197-203	Excluded: not a systematic review or a randomised controlled trial
Ward Nicholas T, Darracq Michael A, Tomaszewski Christian, and Clark Richard F (2012) Evidence-based treatment of jellyfish stings in North America and Hawaii. Annals of emergency medicine 60(4), 399-414	Excluded: outcomes not relevant
Yeo A W. C (2007) From bites to foreign bodies. Paediatrics, and Child and Adolescent Health 47(1), 7-11	Excluded: study could not be retrieved
Yuen E C. P (2004) The use of prophylactic antibiotics in trauma. Hong Kong Journal of Emergency Medicine 11(3), 161-168	Excluded: not a systematic review or a randomised controlled trial
Zehtabchi S (2007) The role of antibiotic prophylaxis for prevention of infection in patients with simple hand lacerations. Annals of Emergency Medicine 49(5), 682-689	Excluded: population not relevant