National Institute for Health and Care Excellence

NICE guideline NG190

Secondary bacterial infection of eczema and other common skin conditions: antimicrobial prescribing guideline

Evidence review

March 2021

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1 Context

1.1 Background

Breaks in the skin caused by common skin conditions are particularly susceptible to infection due to bacteria that live on the skin infiltrating the damaged area. The most commonly infected skin conditions are eczema, psoriasis, chickenpox, shingles and scabies.

Eczema is a chronic, itchy, inflammatory skin condition that mainly affects children, although it can affect all ages (Clinical knowledge summary [CKS], eczema – atopic). Atopic eczema is very common, with a prevalence of around 10 to 30% in children and 2 to 10% in adults, with prevalence increasing. The skin of people with atopic eczema is often heavily colonised with *Staphylococcus aureus,* which represents about 90% of the total aerobic bacteria flora of affected people, compared with 30% in people without atopic eczema (NICE guideline on Atopic eczema in under 12's [CG57]). Clinically infected eczema is associated with *Staphylococcus aureus* or *Streptococcus pyogenes*, which can present as typical impetigo or as worsening of eczema, with increased redness, pustules or purulent exudation with crusting of the skin (NICE guideline on Atopic eczema in under 12's [CG57]). Viral infection with herpes simplex virus (eczema herpeticum) is also well characterised but is not covered by this antimicrobial prescribing guideline (see the NICE guideline on Atopic eczema in under 12's [CG57] for recommendations on this infection).

Psoriasis is an inflammatory skin disease, most commonly characterised by raised, red, scaly patches (plaque psoriasis) or widespread, small, red spots (guttate psoriasis; NICE guideline on Psoriasis [CG153]). Bacterial infection of the superficial layers of the skin is termed erysipelas and infection of the dermis and subcutaneous tissues is termed cellulitis; infected psoriasis may present as either erysipelas or cellulitis, which are often grouped together as cellulitis (CKS, cellulitis – acute). The most common causative pathogens of cellulitis are *Streptococcus pyogenes* and *Staphylococcus aureus.* Other less common organisms include *Streptococcus pneumoniae, Haemophilus influenza,* Gram negative bacilli and anaerobes (NICE guideline on cellulitis and erysipelas [NG141]).

Chickenpox is an acute disease caused by varicella-zoster virus, characterised by a vesicular rash and often fever and malaise (CKS – chickenpox). The most common complication of chickenpox is bacterial infection of the blisters, typically caused by *Staphylococcus aureus* or *Streptococcus pyogenes*. Complications are not common in healthy people who get the disease, but people at higher risk of complications include newborns, adults, pregnant women and people with weakened immune systems.

Shingles is an infection that is characterised by a painful rash. The rash is usually on the thorax, on one side of the body and develops into itchy blisters (NHS – shingles). Shingles is a viral infection of nerve cells, caused by latent varicella-zoster virus reactivating due to a weakened immune system. The severity of shingles increases with age and older adults are more likely to develop severe shingles and secondary complications (CKS – shingles). Secondary infection is usually caused by *Staphylococcal* or *Streptococcal* bacteria, which can result in cellulitis or necrotising fasciitis, scaring or changes in pigmentation.

Scabies is an intensely itchy skin infestation caused by the human parasite *Sarcoptes scabiei,* which develops into a rash (CKS – scabies). Impetigo, folliculitis, furunculosis, ecthyma or abscesses can be caused by secondary bacterial infection of scabies infestation. A study of 30 secondarily infected scabies lesions in children showed aerobic and anaerobic bacteria were present, including *Staphylococcus aureus*, *Streptococcus pyogenes, Pseudomonas aeruginosa, Peptostreptococcus* species*, Prevotella* species and *Porphyromonas* species (Brook et al. 2002).

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 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.

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

1.3 Antimicrobial resistance

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

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

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

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

The ESPAUR report 2019 to 2020 reported that antimicrobial prescribing has been decreasing since its peak in 2014, with the total consumption of antibiotics in primary and

secondary care (measured in terms of new defined daily doses) declining by 7.5% from 2015 to 2019. This reflected a decrease in antibiotic prescribing of 12.2% in GP settings and 19.5% in dental settings, with an increase of 3.5% in secondary care prescribing. In 2019, the most commonly used antibiotics were penicillins (37.8%), tetracyclines (26.4%) and macrolides (15.3%).

Over the 5-year period from 2015 to 2019, significant declining trends of use were seen for some antibiotics, including penicillins (excluding combinations), first and second-generation cephalosporins and macrolides. In contrast, use of third, fourth and fifth generation cephalosporins significantly increased.

Penicillins are the most commonly prescribed antibiotics in England, accounting for 37.8% of total antibiotic prescribing in 2019. Over the last 5-years, consumption has decreased by 8.3% overall, and 13.6% in GP settings. Total consumption of macrolides has decreased by 15.5% from 2015 to 2019. The most commonly used macrolide was clarithromycin, although its use in both primary and secondary care has steadily declined since 2016.

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 secondary bacterial skin infections (see appendix C: literature search strategy for full details). The literature search identified 3,328 references and 1 reference was identified through an additional source (an updated version of a Cochrane review identified in the search). These references were screened using their titles and abstracts and 54 full text references were obtained and assessed for relevance. Five full text references of systematic reviews and 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. All 5 references were included in this evidence review (see appendix E: included studies).

The remaining 49 references were excluded. These are listed in appendix H: excluded studies with reasons for their exclusion.

See also appendix D: study flow diagram.

2.2 Summary of included studies

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

Table 1: Summary of included studies

Study	Number of participants	Population	Intervention	Comparison	Key outcomes
Francis et al. 2016* RCT	N=113	Children aged 3 months to <8 years with atopic eczema who presented with clinically suspected infected eczema. This included children where: • the eczema was failing to respond to standard treatment with emollients and/or mild to moderate topical corticosteroids • there was a flare in the severity or extent of the eczema • there was weeping or crusting.	3-armed trial comparing oral antibiotics, topical antibiotics and placebo. Oral antibiotic arm: • flucloxacillin suspension (erythromycin if penicillin allergic, but no penicillin allergic children were randomised to this arm) • placebo topical cream Topical antibiotic arm: • fusidic acid cream • placebo oral suspension	Placebo arm: • placebo topical cream • placebo oral suspension	Primary outcome: • Subjective severity at 2 weeks using Patient Orientated Eczema Measure Secondary outcomes: • Subjective eczema severity at 4 weeks and 3 months • Objective eczema severity using Eczema Area and Severity Index • Quality of life using Infants' Dermatitis Quality of Life and Children's Dermatology Life Quality Index
George et al. 2019 Systematic review	5 relevant studies included, N=290 (total N=1,753 41 studies)	Children, young people and adults with mild to severe eczema. Relevant studies included people (children or age not reported) with infected eczema. Population colonised with S. aureus was not reported in 1 included RCT, and was 79%,	Oral antibiotic	Placebo	• Global improvement in symptoms or signs • Quality of life • Severe adverse events requiring withdrawal • Minor adverse events
			Topical antibiotic plus topical corticosteroid	Topical corticosteroid	
			Intranasal antibiotic plus bleach bath	Placebo	
			Antiseptic emollient	Placebo	

Study	Number of participants	Population	Intervention	Comparison	Key outcomes
		87% and 100% in the other 3 RCTs in the SR.			• Emergence of antibiotic-resistant micro-organisms
Larsen et al. 2007 RCT	Total population N=629 (n=254 in 2 groups included in this review)	Children ≥6 years, young people and adults with clinically infected eczema based on clinical evaluation.	Fusidic acid plus betamethasone cream	Lipid cream vehicle	• Total severity score • Treatment efficacy • Microbiological assessment • Adverse events
Pratap et al. 2013 RCT	N=152	Adults with infected acute or chronic eczema.	Fusidic acid plus halometasone cream	Neomycin plus betamethasone cream	• Objective eczema severity using Eczema Area and Severity Index and Investigator Global Assessment • Adverse events
Rist et al. 2002 RCT	N=159	Adults and children ≥8 years with secondarily infected eczema.	Oral cephalexin plus cream placebo	Topical mupirocin cream plus oral placebo	• Clinical response at end of treatment • Bacteriological response • Adverse events

Abbreviations: RCT, randomised controlled trial

*this trial was also included in George 2019 Systematic review, but the comparison of topical vs. oral was not included in George 2019, therefore the paper was assessed individually for this comparison. The comparison of topical v placebo and oral vs. placebo for Francis 2016 are included in George 2019.

3 Evidence summary

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

The main results are summarised below for adults, young people and children with infected secondary skin infections.

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 Efficacy of antibiotics

3.1.1 Oral antibiotics

The evidence for the efficacy of oral antibiotics for infected secondary skin infections comes from 1 systematic review and meta-analysis (George et al. 2019), which included 2 randomised controlled trials (RCTs) relevant for this comparison (Francis et al. 2016 and Weinberg et al. 1992). Participants in the relevant studies had clinically suspected infection of eczema or confirmed secondary infection of eczema (including *Staphylococcus aureus* 'super infection'). The average age of participants was 3 in one study and 4.4 years in the other study. *Staphylococcus aureus* colonisation was reported in most participants. The severity of the underlying skin condition (eczema) was not reported. Participants with severe infection or significant comorbid illness were excluded from Francis et al. 2016.

Oral antibiotics compared with placebo

A systematic review (George et al. 2019) found that oral antibiotics (either flucloxacillin or cefadroxil) were not significantly different to placebo in children with infected eczema for the number of people in whom *Staphylococcus aureus* was isolated at the end of treatment (2 RCTs, n=98, 46.8% versus 56.9%, relative risk [RR] 0.70, 95% confidence interval [CI] 0.22 to 2.23; very low quality evidence).

There was no significant difference between oral antibiotics and placebo in the number of children experiencing adverse events requiring withdrawal from treatment (2 RCTs, n=109, 3.8% versus 1.8%, RR 1.75, 95% CI 0.22 to 13.73; very low quality evidence).

Oral antibiotics used in this comparison included flucloxacillin suspension (250 mg/5 ml, 2.5 ml four times a day [children aged 3 months to 2 years] or 5 ml four times a day [children aged >2 years to <8 years]) for 7 days or cefadroxil (50 mg/kg/day in 2 equal doses for 14 days). Participants in all arms in 1 RCT (Francis et al. 2016; totalling 70% of participants in this comparison) were given topical corticosteroids (clobetasone butyrate 0.05% cream or ointment for use on trunk and limbs, and/or hydrocortisone 1% cream or ointment for use on face, applied once a day for 14 days) and were encouraged to use emollients.

See GRADE profile: Table 4

Oral flucloxacillin compared with placebo

A systematic review (George et al. 2019) found that oral flucloxacillin was not significantly different to placebo in children with infected eczema for quality of life at end of treatment or at 3 months:

- mean difference in Infants' Dermatitis Quality of Life [IDQoL] score at 3 months: 1 RCT, n=45, mean difference 0.11 higher [worse] with oral flucloxacillin, 95% CI −0.1 to 0.32, moderate quality evidence
- mean difference in Children's Dermatology Life Quality Index [CDLQI] score at 3 months: 1 RCT, n=14, mean difference 0.14 lower [better] with oral flucloxacillin, 95% CI −0.97 to 0.69, moderate quality evidence.

There was no significant difference between oral flucloxacillin and placebo in children with infected eczema for eczema severity scores (Patient Orientated Eczema Measure [POEM] and Eczema Area and Severity Index [EASI]) at the end of treatment (both scores) or at 3 months (POEM only):

- mean difference in POEM score at end of treatment: 1 RCT, n=70, mean difference 1.52 higher [worse] with oral flucloxacillin, 95% CI −1.36 to 4.40, low quality evidence
- mean difference in EASI score at end of treatment: 1 RCT, n=68, mean difference 0.20 higher [worse] with oral flucloxacillin, 95% CI −0.12 to 0.52, moderate quality evidence
- mean difference in POEM score at 3 months: 1 RCT, n=53, mean difference 0.21 lower [better] with oral flucloxacillin, 95% CI −3.12 to 2.70, moderate quality evidence).

There was also no significant difference between oral flucloxacillin and placebo in children with infected eczema for the change from baseline in isolation rate of *Staphylococcus aureus* at end of treatment or at 3 months (1 RCT, n=51, mean difference at 3 months 32.6% lower [better] with oral flucloxacillin, 95% CI −65.92% to 0.72%, low quality evidence).

There were no significant differences between flucloxacillin and placebo for minor patient-reported adverse events (including nausea, vomiting, diarrhoea, stomach pain and joint pain).

The flucloxacillin dose was 125 mg given in 2.5 ml of suspension for children aged 3 months to 2 years or 250 mg given in 5 ml for children aged 2 to 8 years, four times a day for 7 days. Participants in both arms were also given topical corticosteroids and were encouraged to use emollients as outlined above.

See GRADE profile: Table 5

Oral cefadroxil compared with placebo

A systematic review (George et al. 2019) found that oral cefadroxil (50 mg/kg/day in 2 equal doses for 14 days) was not significantly different to placebo for children with *S. Aureus* superinfected atopic dermatitis for achieving global evaluation of improvement of good or excellent at end of treatment (1 RCT, n=29, 83.3% versus 52.9%, RR 1.57, 95% CI 0.94 to 2.63, very low quality evidence) or presence of erythema at end of treatment (1 RCT, n=30, 38.5% versus 41.2%, RR 0.93, 95% CI 0.38 to 2.28, very low quality evidence).

Oral cefadroxil was more effective than placebo in children with infected eczema for reducing presence of clinically apparent infection at end of treatment (1 RCT, n=28,

0.0% versus 60%, RR 0.06, 95% CI 0.00 to 0.94, NNT 2 [2 to 3], very low quality evidence).

There was one withdrawal in the oral antibiotic group due to an adverse event, but the nature of the event was not specified.

See GRADE profile: Table 6

3.1.2 Topical antibiotics

The evidence for efficacy of topical antibiotics for infected secondary skin infections comes from 1 systematic review and meta-analysis (George et al. 2019), which included 3 RCTs relevant for this comparison (Francis et al. 2016, Huang et al. 2009 and Wachs et al. 1976). Participants in the relevant studies had secondary infection of eczema (defined in Huang et al. 2009 as weeping, crusting and/or pustules) or clinically suspected infection of eczema. The average age of participants ranged was 3 years, 8 years or was not reported. *Staphylococcus aureus* colonisation was reported in most participants. Participants included in Huang et al. 2009 had moderate to severe eczema; the severity of eczema was not reported in the other relevant studies. Participants with severe infection or significant comorbid illness were excluded from Francis et al. 2016, and participants with symptoms requiring oral antibiotics or corticosteroids were excluded from Wachs et al. 1976.

Topical antibiotic plus topical corticosteroid compared with topical corticosteroid

A systematic review (George et al. 2019) found that a topical antibiotic plus a topical corticosteroid was not significantly different to a topical corticosteroid alone in people with infected eczema for the isolation of *Staphylococcus aureus* at end of treatment (2 RCTs, n= 107, 26.8% versus 32.8%, RR 0.80, 95% [CI 0.47 to 1.38], very low quality evidence).

Topical antibiotics plus corticosteroids used in this comparison included topical fusidic acid 2% cream, 3 times a day for 7 days plus topical corticosteroids (clobetasone butyrate 0.05% cream or ointment for use on trunk and limbs and/or hydrocortisone 1% cream or ointment for use on face, applied once a day for 14 days) and encouraged to use emollients; or, topical gentamicin and betamethasone valerate cream, applied 3 times a day for 22 days. The topical corticosteroid alone arm used the same corticosteroid and emollient treatment as the intervention arm, with or without the use of a placebo and without the addition of topical fusidic acid or gentamicin.

No safety or tolerability data was reported.

See GRADE profile: Table 7

Topical fusidic acid plus topical corticosteroid compared with placebo plus topical corticosteroid

A systematic review (George et al. 2019) found that topical fusidic acid plus a topical corticosteroid was not significantly different to placebo plus a topical corticosteroid in children with infected eczema for change from baseline in Infants' Dermatitis Quality of Life (IDQoL) at end of treatment or at 3 months (1 RCT, n=31, mean difference at 3 months: 0.07 lower [better] with topical fusidic acid plus topical corticosteroid, 95% CI −0.31 to 0.17, moderate quality evidence).

Topical fusidic acid plus a topical corticosteroid was less effective than placebo plus a topical corticosteroid in children with infected eczema for change from baseline in Children's Dermatology Life Quality Index (CDLQI) score at end of treatment (1 RCT, n=23, mean difference 0.70 higher [worse] with topical fusidic acid plus topical corticosteroid, 95% CI 0.12 to 1.28, low quality evidence), but there was no significant difference in change from baseline in CDLQI for the same comparison at 3 months (1 RCT, n=14, mean difference 0.13 lower [better] with topical fusidic acid plus topical corticosteroid, 95% CI −0.96 to 0.70, moderate quality evidence).

There was no significant difference between topical fusidic acid plus a topical corticosteroid compared with placebo plus a topical corticosteroid in children with infected eczema for Patient Orientated Eczema Measure (POEM) at end of treatment or at 3 months (1 RCT, n=46, mean difference at 3 months: 1.13 lower [better] with topical fusidic acid plus topical corticosteroid, 95% CI −4.32 to 2.06, low quality evidence).

Topical fusidic acid plus a topical corticosteroid was less effective than placebo plus a topical corticosteroid in children with infected eczema for change from baseline in Eczema Area and Severity Index (EASI) at end of treatment (1 RCT, n=65, mean difference 0.42 higher [worse] with topical fusidic acid plus a topical corticosteroid, 95% CI 0.09 to 0.75, moderate quality evidence).

There was no significant difference between topical fusidic acid plus a topical corticosteroid compared with placebo plus a topical corticosteroid in children with infected eczema for the mean value of composite rating scale at end of treatment (1 RCT, n=65, standard mean difference 0.42 higher [worse] with topical fusidic acid plus topical steroid, 95% CI −0.07 to 0.91, moderate quality evidence).

Staphylococcus aureus isolated from the skin, nose and mouth at end of treatment (2 weeks) and at 3 months was tested for resistance to flucloxacillin, erythromycin and fusidic acid. There were no differences in the number of people with antibiotic resistance for all outcomes. There was no significant difference between topical fusidic acid plus a topical corticosteroid compared with placebo plus a topical corticosteroid in children with infected eczema for the change from baseline in isolation rate of *Staphylococcus aureus* at end of treatment (1 RCT, n=65, mean difference at 2 weeks: 15.3% lower [better] with topical fusidic acid, 95% CI −48.43% to 17.83%, low quality evidence) or at 3 months (1 RCT, n=46, mean difference at 3 months: 8.6% lower [better] with topical fusidic acid, 95% CI −45.44% to 28.24%, very low quality evidence).

There was no significant difference between topical fusidic acid plus a topical corticosteroid compared with placebo plus a topical corticosteroid in children with infected eczema in the number reporting adverse events requiring withdrawal from treatment (1 RCT, n=73, 13.5% versus 2.5%, RR 5.41, 95% CI 0.66 to 44.14, very low quality evidence).

Treatment used in this comparison included topical fusidic acid 2% cream, 3 times a day for 7 days plus topical corticosteroids (clobetasone butyrate 0.05% cream or ointment for use on trunk and limbs and/or hydrocortisone 1% cream or ointment for use on face, applied once a day for 14 days) and encouragement to use emollients compared with topical corticosteroids and encouragement to use emollients as in treatment group.

See GRADE profile: Table 8

Topical gentamicin plus topical corticosteroid compared with topical corticosteroid

A systematic review (George et al. 2019) found that topical gentamicin plus a topical corticosteroid (topical gentamicin plus betamethasone valerate cream [dose not reported], applied 3 times a day for 22 days) was not significantly different to a topical corticosteroid alone (betamethasone valerate cream, applied 3 times a day for 22 days) in people with infected eczema for:

- global outcome of improvement of symptoms or signs (patient or physician rated) good or excellent at end of treatment (1 RCT, n= 52, 92.0% versus 74.1%, RR 1.24, 95% CI 0.97 to 1.60, low quality evidence).
- number of patients in whom *S. aureus* was isolated at end of treatment (1 RCT, n=52, 16% versus 14.8%, RR 1.08 95% CI 0.30 to 3.86, very low-quality evidence).

There was a mean reduction in inflammation score (out of 10) for both groups: the score reduced from 5.8 to 0.7 in the betamethasone valerate plus gentamicin group compared with 5.9 to 1.4 in the betamethasone valerate-only group. Standard deviations not reported, no further information was available.

No safety or tolerability data was reported.

See GRADE profile: Table 9

3.1.3 Antibacterial bath plus antibiotic compared with water plus placebo

Topical mupirocin plus bleach bath compared with placebo

A systematic review (George et al. 2019) found that intranasal mupirocin plus a bleach bath was more effective than placebo in children with infected eczema for change from baseline in EASI at 1 month and 3 months (1 month: 1 RCT, n=25, mean difference 7.9 lower [better] with intranasal mupirocin plus bleach bath, 95% CI −14.22 to −1.58, low quality evidence; 3 months: 1 RCT, n=22, mean difference 12.1 lower [better] with intranasal mupirocin plus bleach bath, 95% CI −20.18 to −4.02, low quality evidence).

Intranasal mupirocin plus a bleach bath was also more effective than placebo in children with infected eczema for number of children with a reduction in Investigator Global Assessment (IGA) at 3 months (1 RCT, n=22, 66.7% versus 15.4%, RR 4.33, 95% CI 1.12 to 16.82, NNT 2 [2 to 7] low quality evidence).

There was no significant difference between intranasal mupirocin plus bleach bath compared with placebo in children with infected eczema for any microbiology outcomes, including:

- the number of people in whom methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated at 1 or 3 months (3 months: 1 RCT, n=21, 12.5% versus 7.7%, RR 1.63, 95% CI 0.12 to 22.5, very low-quality evidence)
- number of people in whom *Staphylococcus aureus* was isolated at 1 or 3 months (3 months: 1 RCT, n=21, 87.5% versus 79.9%, RR 1.14, 95% CI 0.77 to 1.69, low quality evidence).

Intranasal mupirocin plus bleach bath treatment used in this comparison was mupirocin ointment (dose not reported) applied intranasally twice a day for 5 consecutive days of each month, plus half a cup of 6% bleach in a full bathtub (40 gallons) of water (final concentration bleach 0.005%) for bathing in 5 to

10 minutes twice weekly. Placebo treatment was petrolatum ointment applied intranasally twice a day for 5 consecutive days of each month, plus water added to a full bath for bathing in 5 to 10 minutes twice weekly.

No participants withdrew from treatment due to adverse events. One participant in the treatment group experienced itching and irritation of the skin.

See GRADE profile: Table 10

3.2 Efficacy of antibiotic and steroid combination

3.2.1 Topical antibiotic plus topical corticosteroid

The evidence for efficacy of antibiotic and topical steroid combination for infected secondary skin infections comes from 1 randomised controlled trial (RCT; Larsen et al. 2007). Participants were ≥6 years and had a clinical diagnosis of secondary infection of eczema, including slight to severe signs of erythema, oedema, oozing and excoriation. The average age of participants was 25 years. *Staphylococcus aureus* colonisation was identified from over half (66%) of participants, either alone or in combination with beta-haemolytic streptococci; beta-haemolytic streptococci was found in isolation in only 5 (0.8%) of participants.

Topical fusidic acid plus topical corticosteroid compared with placebo

One RCT (Larsen et al. 2007) found that a topical fusidic acid plus topical corticosteroid combination (fusidic acid [20 mg/g] and betamethasone valerate [91 mg/g] in a lipid cream, applied twice a day for 14 days) was more effective than placebo (lipid cream vehicle, applied twice a day for 14 days) in people with infected eczema for:

- total severity score at end of treatment (1 RCT, n=365, mean percentage reduction 82.7% versus 33.0%, estimated treatment difference 48.3%, 95% confidence interval [CI] 41.0% to 55.7%, p<0.001, moderate quality evidence)
- the number of responders (with marked improvement or complete clearance) at the end of treatment (1 RCT, n=365, 83.6% versus 31.1%, relative risk [RR] 2.69, 95% CI 1.97 to 3.67, NNT 2 [2 to 3], high quality evidence)
- the number of people with successful biological response (baseline pathogen eradication or no visible target lesions) at end of treatment (1 RCT, n=365, 87.6% versus 25.6%, RR 3.43, 95% CI 2.40 to 4.89, NNT 2 [2 to 2], high quality evidence).

There was no significant difference between topical fusidic acid plus corticosteroid combination compared with placebo in people with infected eczema for:

- the number of *Staphylococcus aureus* isolates resistant to fusidic acid at the end of treatment (1 RCT, n=357, 2.3% versus 1.9%, RR 1.25, 95% CI 0.16 to 9.94, low quality evidence).
- the number of people reporting adverse events (1 RCT, n=362, 13.5% versus 21.6%, RR 0.63, 95% CI 0.38 to 1.03, moderate quality evidence)

However, less people reported adverse drug reactions with topical fusidic acid with corticosteroid compared to placebo (1 RCT, n= 362, 2.6% versus 13.6%, RR 0.19, 95% CI 0.08 to 0.46, high quality evidence).

See GRADE profile: Table 11

3.3 Efficacy of antiseptics

3.3.1 Antiseptic emollient

The evidence for efficacy of antiseptics comes from 1 systematic review and meta-analysis (George et al. 2019), which included 1 randomised controlled trial (RCT) relevant for this comparison (Harper et al. 1995). Participants in the relevant study had eczema displaying features of recurrent infection and/or frequent exacerbations. The mean age was 4.5 years. Limited statistical data was presented for this comparison due to poor reporting in the primary study.

Triclosan and benzalkonium chloride emollient compared with non-antimicrobial emollient

A systematic review (George et al. 2019) compared triclosan and benzalkonium chloride emollient (Oilatum Plus; 15 ml diluted in bath water for 10 to 15 minute soak once a day for 4 weeks) to a non-antimicrobial emollient (Oilatum; 15 ml diluted in bath water for 10 to 15 minute soak once a day for 4 weeks) in children with recurrent infection or frequent exacerbations of eczema for global degree of improvement in symptoms; but no conclusions could be drawn due to the study not reporting data (no data reported, very low quality evidence).

One participant in each study arm withdrew from treatment because of adverse events (n=26; number of participants in each arm unclear, very low-quality evidence). Minor adverse events were reported by 3 participants in the triclosan and benzalkonium chloride emollient arm, compared with 5 in the non-antimicrobial emollient arm (very low-quality evidence).

See GRADE profiles: Table 12

3.4 Choice of antibiotic

3.4.1 Topical antibiotics

The evidence for choice of topical antibiotic for secondary skin infection comes from 1 randomised controlled trial (RCT; Pratap et al. 2013). Participants were over 18 years and had either acute or chronic eczema which was infected.

Fusidic acid plus topical corticosteroid compared with neomycin plus topical corticosteroid

An RCT (Pratap et al. 2013) found that fusidic acid plus a topical corticosteroid was not significantly different to neomycin plus a topical corticosteroid in adults with infected eczema for Eczema Area and Severity Index (EASI) at first evaluation (day 5 for people with acute eczema or day 10 for people with chronic eczema), second evaluation (day 10 [acute eczema] or day 20 [chronic eczema]) or end of treatment (day 20 [acute eczema] or day 30 [chronic eczema]. EASI at end of treatment: 1 RCT, n=142, mean difference 0.22 lower [better] with fusidic acid plus topical corticosteroid, 95%CI −0.58 to 0.14, moderate quality evidence).

There was also no significant difference between fusidic acid plus a topical corticosteroid compared with neomycin plus a topical corticosteroid in adults with infected eczema for Investigator Global Assessment (IGA) at first or second evaluation or at end of treatment (IGA at end of treatment: 1 RCT, n=142, mean

difference 0.1 lower [better] with fusidic acid plus topical corticosteroid, 95% CI –0.35 to 0.15, moderate quality evidence).

There was no significant difference between fusidic acid plus a topical corticosteroid compared with neomycin plus a topical corticosteroid in adults with infected eczema achieving relief of individual symptoms such as itching and pruritus, or the number of people achieving cure or improvement at end of treatment (cure at end of treatment: 1 RCT, n=142, 54.3% versus 50.0%, RR 1.09, 95% CI 0.79 to 1.49, low quality evidence).

Fusidic acid plus a topical corticosteroid was more effective than neomycin plus a topical corticosteroid in adults with infected eczema for the number of people with positive bacterial culture at day 10 and end of treatment (1 RCT, n=129, day 10 25.8% versus 56.7%, RR 0.46 95% CI 0.28 to 0.73, NNT 3 [2 to 7]) moderate quality evidence; end of treatment 16.1% versus 34.3%, RR 0.47, 95% CI 0.24 to 0.91, NNT 6 [3 to 28] low quality evidence).

There was no significant difference between fusidic acid plus a topical corticosteroid compared with neomycin plus a topical corticosteroid in adults with infected eczema in the number of people reporting adverse events (1 RCT, n=152, 3.9% versus 2.7%, RR 1.46, 95% CI 0.25 to 8.50, very low quality evidence).

Antibiotics plus a topical corticosteroid used in this comparison were fusidic acid 2% plus halometasone 0.05% cream, or neomycin sulfate 0.5% plus betamethasone 0.12%, applied twice a day without any occlusive bandage to the eczematous skin, using enough to cover the entire affected area lightly. People with acute eczema were treated for 20 days, people with chronic eczema were treated for 30 days.

See GRADE profiles: Table 13

3.5 Route of administration

3.5.1 Oral antibiotic compared with topical antibiotic

The evidence for oral antibiotics compared with topical antibiotics for secondary skin infection comes from 2 randomised controlled trials (RCTs; Francis et al. 2016 and Rist et al. 2002). One RCT (Francis et al. 2016) only included children, with a mean age of 3 years; the average age of participants in Rist et al. 2002 was 43 years (range 9 to 87 years). People were included if they had or were suspected of having secondarily infected eczema, described by Francis et al. 2016 as eczema failing to respond to standard treatment, flares in the severity or extent of eczema or weeping and crusting; most participants (92%) in Francis et al. 2016 had weeping, crusting, pustules or painful skin.

Oral flucloxacillin compared with topical fusidic acid

An RCT (Francis et al. 2016) found that oral flucloxacillin was not significantly different to topical fusidic acid in children with infected eczema for any clinical outcomes. Clinical outcomes included Patient Orientated Eczema Measure (POEM), Eczema Area and Severity Index (EASI), Dermatitis Family Impact (DFI), Infants' Dermatitis Quality of Life (IDQoL) and Children's Dermatology Life Quality Index (CDLQI) scores and the number of children with *Staphylococcus aureus* on the skin after treatment. Most outcomes were measured at end of treatment (2 weeks), 4 weeks and 3 months.

At 3 months there was no significant difference between oral flucloxacillin and topical fusidic acid in POEM score (1 RCT, n= 65, mean difference 0, 95%CI −3.37 to 3.37, moderate quality evidence), DFI score (1 RCT, n=45, mean difference 0.64 lower [better] with oral flucloxacillin, 95% CI −3.61 to 2.33, low quality evidence), IDQoL score (1 RCT, n=33, mean difference 0.66 lower [better] with oral flucloxacillin, 95% CI -2.95 to 1.63, low quality evidence), CDLQI score (1 RCT, n=12, mean difference 0.96 higher [worse] with oral flucloxacillin, 95% CI −5.56 to 7.48, very low quality evidence) or the number of people with *Staphylococcus aureus* isolated from the skin (1 RCT, n=47, 30.8% versus 38.1%, RR 0.81, 95% CI 0.37 to 1.79, very low quality evidence). EASI score was measured at 4 weeks, and there was no significant difference between oral flucloxacillin and topical fusidic acid (1 RCT, n=66, mean difference 1.75 lower [better] with oral flucloxacillin, 95% CI −4.53 to 1.03, low quality evidence).

There was also no significant difference between oral flucloxacillin and topical fusidic acid in children with infected eczema for any of the adverse event outcomes reported, including vomiting (1 RCT, n=62, 12.1% versus 6.9%, RR 1.76, 95% CI 0.35 to 8.90, very low quality evidence), diarrhoea (1 RCT, n=62, 15.2% versus 17.2%, RR 0.88, 95% CI 0.28 to 2.73, very low quality evidence), tummy pain, joint pains and new rash.

Staphylococcus aureus isolated from the skin, nose and mouth at end of treatment (2 weeks) and at 3 months was tested for resistance to flucloxacillin, erythromycin and fusidic acid. There were no differences in the number of people with antibiotic resistance for all outcomes, except for people treated with topical fusidic acid who had significantly greater resistance to fusidic acid in isolates taken from the skin compared with people treated with oral flucloxacillin at 2 weeks (1 RCT, n=29, 72.7% versus 5.6%, RR 8.00, 95% CI 1.19 to 53.67, NNH 2 [1 to 2], moderate quality evidence). However, there was no significant difference in resistance to fusidic acid in isolates taken from the skin at 3 months.

There was no significant difference between oral flucloxacillin and topical fusidic acid in children with infected eczema for any healthcare utilisation outcomes, including the number of people with any primary care consultations in the 4 weeks from beginning of treatment (1 RCT, n=63, 42.4% versus 40.0%, RR 1.06, 95% CI 0.59 to 1.92, very low quality evidence) or in the 5 to 12 weeks from beginning of treatment (1 RCT, n=47, 69.2% versus 61.9%, RR 1.12, 95% CI 0.73 to 1.71, very low quality evidence). There was also no significant difference in the number of people with any secondary care consultations in the 4 weeks from beginning of treatment (1 RCT, n=63, 3.0% versus 10.0%, RR 0.30, 95% CI 0.03 to 2.76, very low quality evidence) or in the 5 to 12 weeks from beginning of treatment (1 RCT, n=47, 15.4% versus 9.5%, RR 1.62, 95% CI 0.33 to 7.98, very low quality evidence).

There was no significant difference between oral flucloxacillin and topical fusidic acid in children with infected eczema for the number of follow-up prescriptions for oral or topical antibiotics (oral prescriptions: 1 RCT, n=33, 18.2% versus 21.2%, RR 0.86, 95% CI 0.32 to 2.28, very low quality evidence; topical prescriptions: 1 RCT, n=33, 3.0% versus 14.3%, RR 0.50, 95% CI 0.05 to 5.25, very low quality evidence).

Treatments used in this comparison included flucloxacillin suspension (250 mg/5 ml, 2.5 ml four times a day [children aged 3 months to 2 years] or 5 ml four times a day [children aged >2 years to <8 years]) and fusidic acid 2% cream applied to affected area(s) three times a day for 7 days. All participants also received topical corticosteroids (clobetasone butyrate 0.05% cream or ointment for use of trunk/limbs and/or hydrocortisone 1% cream or ointment for use on face, applied once a day for 14 days) and were encouraged to use emollients.

See GRADE profiles: Table 14, Table 15 and Table 16

Oral cefalexin compared with topical mupirocin

An RCT (Rist et al. 2002) found that oral cefalexin (250 mg four times a day plus topical placebo for 10 days) was not significantly different to topical mupirocin (2% cream three times a day plus oral placebo for 10 days) in people with infected eczema for clinical success at end of treatment (intention to treat population: 1 RCT, n=159, 57.1% versus 63.4%, RR 0.90, 95% CI 0.70 to 1.16, low quality evidence).

However, oral cefalexin was not as effective as topical mupirocin in people with infected eczema for bacteriological eradication or improvement at the end of treatment (1 RCT, n=95, 50.0% versus 27.7%, RR 2.11, 95% CI 1.25 to 3.55, NNT 5 [3 to 31], low quality evidence).

There was no significant difference between oral cefalexin and topical mupirocin in people with infected eczema who had *Staphylococcus aureus* isolated at pre-therapy in the number of *Staphylococcus aureus* isolates eradicated or improved at end of therapy. However, fewer people had *Staphylococcus aureus* isolates persistently eradicated or improved at follow-up (7 to 9 days after end of treatment) with oral cefalexin compared to topical mupirocin (1 RCT, n=74, 54.1% versus 29.7%, RR 1.82, 95% CI 1.02 to 3.24, NNT 5 [3 to 40], low quality evidence). There was no significant difference between treatments for eradication of any other bacterial isolates.

There was no significant difference between oral cefalexin and topical mupirocin in people with infected eczema for the number of people reporting adverse events (1 RCT, n=159, 13.0% versus 8.5%, RR 1.52, 95% CI 0.61 to 3.80, very low-quality evidence) or the number of people reporting application site reactions (1 RCT, n=159, 0% versus 2.4%, RR 0.21, 95% CI 0.01 to 4.36, very low quality evidence).

Patient preference for treatment was 65.5% (n=95/145) preferred topical, 34.4% (n=50/145) preferred oral and 9.7% (n=14/145) did not state a preference (1 RCT, very low-quality evidence).

See GRADE profile: Table 17

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?	• Clinical knowledge summary, eczema – atopic • NICE guideline CG57: Atopic eczema in under 12's • NICE guideline CG153: Psoriasis • Clinical knowledge summary, cellulitis - acute • NICE guideline NG141: Cellulitis and erysipelas • Clinical knowledge summary, chickenpox • NHS inform, Scotland • NHS – Shingles • Clinical knowledge summary, shingles • Clinical knowledge summary, scabies • Brook et al. 2002 • NICE guideline NG15: antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • NICE guideline NG63: antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • Public Health England – Start Smart Then Focus
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: antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • Committee experience

Key area	Key question(s)	Evidence sources
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 (2019)
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 • British National Formulary for children • Summary of product characteristics

Appendix B: Review protocol

Field (based on PRISMA-P)	Content
Review question	What antimicrobial interventions are effective in managing a secondary bacterial infection of a common skin condition, such as eczema?
Types of review question	Intervention
Objective of the review	To determine the effectiveness of antimicrobial prescribing interventions for managing a secondary bacterial infection of a common skin condition, such as eczema to address antimicrobial resistance. In line with the major goals of antimicrobial stewardship 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	Population: Adults and children (aged 72 hours and older) who have a bacterial infection of pre-existing psoriasis, eczema, chickenpox, shingles or scabies.
Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	The review will include studies which include: • Antimicrobial pharmacological interventions[1], alone or in combination with other treatments where antimicrobial is the active component For the treatment of a bacterial infection complicating skin and soft tissue conditions 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	a) Infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) b) Time to clinical cure (mean or median time to resolution of illness) c) Reduction in symptoms (duration or severity) d) Rate of complications with or without treatment e) safety, tolerability, and adverse effects. f) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. g) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. h) Health and social care related quality of life i) Health and social care utilisation (including length of stay, planned and unplanned contacts). The Committee considered which outcomes should be prioritised when there are multiple outcomes, or outcomes at multiple time points are reported.
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

	• non-pharmacological or non-antimicrobial pharmacological interventions (these will be included as comparators). • management of the primary skin condition, for example management of eczema, chicken pox, psoriasis or scabies that does not have a secondary infection • eczema herpeticum
Proposed sensitivity or sub-group analysis	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 be 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. 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-analysis 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.

Appendix C: Literature search strategy

Main concepts	Concept	Proposed search terms
Condition	Bacterial infection of Eczema Bacterial infection of Psoriasis Bacterial infection of chicken pox Bacterial infection of shingles Bacterial infection of scabies	exp ECZEMA/ eczema*.ti,ab. Dermatitis, Atopic/ (dermatit* adj1 atopic*).ti,ab. psoriasis/ or arthritis, psoriatic/ (psoriasis* or psoriatic*).ti,ab. Soft Tissue Infections/
Named Antibiotics	Amikacin	Amikacin/ Amikacin*.ti,ab.
	Amoxicillin	exp Amoxicillin/ Amoxicillin*.ti,ab.
	Ampicillin	Ampicillin/ Ampicillin*.ti,ab
	Azithromycin	Azithromycin/ (Azithromycin* or Azithromicin* or Zithromax*).ti,ab

	Benzylpenicillin sodium	Penicillin G/ (Benzylpenicillin* or "Penicillin G").ti,ab
	Ceftaroline fosamil	(Ceftaroline* or Zinforo*).ti,ab
	Clarithromycin	Clarithromycin/ (Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab
	Chloramphenicol	Chloramphenicol/ (Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab.
	Clindamycin	Clindamycin/ (Clindamycin* or Dalacin* or Zindaclin*).ti,ab
	Co-amoxiclav	Amoxicillin-Potassium Clavulanate Combination/ (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
	Doxycycline	Doxycycline/ (Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab
	Ertapenem	(Ertapenem* or Invanz*).ti,ab
	Erythromycin	Erythromycin/ Erythromycin Estolate/ Erythromycin Ethylsuccinate/ (Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab
	Flucloxacillin	Floxacillin/ (Floxacillin* or Flucloxacillin*).ti,ab.
	Framycetin	Framycetin/ Framycetin*.ti,ab
	Fusidic acid	Fusidic Acid/

		("Fusidic acid" or fusidate or Fucidin).ti,ab.
	Gentamicin	Gentamicins/ (Gentamicin* or Gentamycin* or Cidomycin*).ti,ab
	Imipenem	Imipenem/ (Imipenem* or Primaxin*).ti,ab
	Levamisole	Levamisole/ (Levamisole* OR ergamisol*).ti,ab
	Levofloxacin	Levofloxacin/ (Levofloxacin* or Evoxil* or Tavanic*).ti,ab.
	Linezolid	Linezolid/ (Linezolid* or Zyvox*).ti,ab
	Meropenem	(Meropenem*).ti,ab
	Metronidazole	Metronidazole/ Metronidazole*.ti,ab.
	Neomycin	exp Neomycin/ (neom?cin* or "Neo-Fradin").ti,ab.
	Mupirocin	Mupirocin/ (Mupirocin* or Bactroban*).ti,ab.
	Ofloxacin	Ofloxacin/ (Ofloxacin* or Tarivid*).ti,ab
	Phenoxymethylpenicillin (penicillin V)	Penicillin V/ (Phenoxymethylpenicillin* or "Penicillin V").ti,ab.
	Piperacillin with Tazobactam	Piperacillin/ (Piperacillin* or Tazobactam* or Tazocin*).ti,ab

	Teicoplanin	Teicoplanin/ (Teicoplanin* or Targocid*).ti,ab
	Tedizolid	Tedizolid*.ti,ab
	Tigecycline	(Tigecycline* or Tygacil*).ti,ab
	Vancomycin	Vancomycin/ (Vancomycin* or Vancomicin* or Vancocin*).ti,ab
Classes of Antibiotics	Aminoglycoside	exp Aminoglycosides/ Aminoglycoside*.ti,ab
	Antipseudomonal penicillin	exp Penicillins/ Penicillin*.ti,ab
	Beta-lactamase	exp beta-Lactamases/ ((beta adj Lactamase*) or betaLactamase* or beta-Lactamase*).ti,ab. exp beta-Lactamase inhibitors/
	Beta-lactam (stable)	beta-Lactams/ (beta-Lactam or betaLactam or beta Lactam or beta-Lactams or betaLactams or beta Lactams).ti,ab.
	Carbapenems	exp Carbapenems/ Carbapenem*.ti,ab
	Cephalosporins	exp Cephalosporins/ Cephalosporin*.ti,ab
	Fluoroquinolones	exp Fluoroquinolones/ Fluoroquinolone*.ti,ab
	Macrolides	exp Macrolides/ macrolide*.ti,ab
	Polymyxins	Polymyxins/

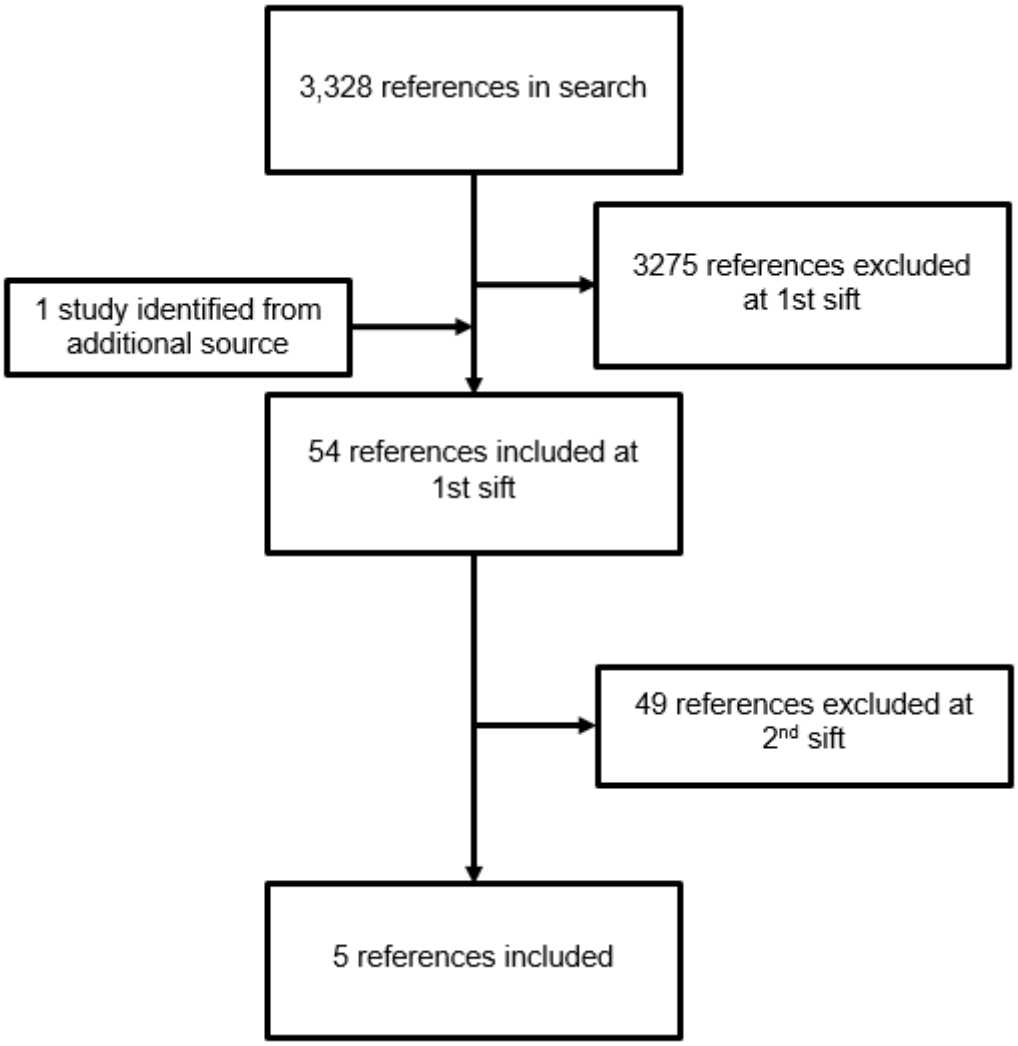
		Polymyxin*.ti,ab
	Quinolones	exp Quinolones/ Quinolone*.ti,ab
	Tetracyclines	exp Tetracyclines/ Tetracycline*.ti,ab
	General terms	anti-infective agents/ or exp anti-bacterial agents/ (antibacter* or anti-bacter* or antibiot* or anti-biot* or antimicrobial* or anti-microbial*).ti,ab.
Interventions – specific antiseptics	Chlorhexidine	Chlorhexidine/ (Chlorhexidine* or Unisept* or Hibiscrub* or Hydrex* or Hibi or HiBiTane*).ti,ab.
	Dialkylcarbamoyl chloride	("Dialkylcarbamoyl chloride" or "Cutimed Sorbact").ti.ab.
	Glucose oxidase	Glucose oxidase/ "Glucose oxidase".ti.ab
	Hydrogen peroxide	Hydrogen Peroxide/ ("Hydrogen peroxide" or crystacide*).ti,ab.
	Lactoperoxidase	Lactoperoxidase/ (Lactoperoxidase* or Flaminal*).ti.ab
	Octenidine	(Octenidine* or Octenilin*).ti.ab.
	Polihexanide	(Polihexanide* or Suprasorb* or Polyhexamethylene*).ti.ab.
	Povidone-iodine	Povidone-Iodine/ (Povidone-Iodine* or Betadine* or Videne* or Inadine*).ti,ab.
	Potassium permanganate	Potassium Permanganate/ ("Potassium permanganate" or "EN-Potab" or Permitabs).ti,ab.

	Proflavine	Proflavine/ Proflavine*.ti,ab.
	Silver sulfadiazine	Silver Sulfadiazine/ (Silver Sulfadiazine* or Flamazine*).ti,ab.
	Antimicrobial reactive oxygen gel/reactive oxygen therapy	(reactive oxygen or surgihoney*).ti,ab
	Triclosan	
	Iodine	Iodine/ (Iodine* or Iodoflex* or Iodosorb* or Iodozyme* or Oxyzyme*).ti,ab
	Honey-based topical application	Honey/ or Apitherapy/ (Apitherap* or Honey* or L-Mesitran or MANUKApli or Medihoney* or Melladerm* or Mesitran*).ti,ab
	Vinegar	
	Bicarbonate of soda	
	Magnesium sulfate paste	
Interventions – general antiseptic terms	General antiseptic terms	exp anti-infective agents, local/ (Antiseptic* or anti-septic* or anti septic* or anti-infective* or anti infective or antiinfective or microbicide*).ti,ab.
Prescribing Strategies	Active surveillance No intervention Watchful waiting	watchful waiting/ "no intervention*".ti,ab (watchful* adj2 wait*).ti,ab. (wait adj2 see).ti,ab

		(expectant* adj2 manage*).ti,ab (active* adj2 surveillance*).ti,ab
	Prescribing times Delayed treatment	Inappropriate prescribing/ ((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab ((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. ((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
Systematic Reviews	Meta analysis Systematic Reviews Reviews	Standard search filter
Randomised Controlled Trials	Controlled Clinical Trials Cross over studies Randomised controlled trials (rcts)	Standard search filter
Observational Studies	Case-Control Studies	Standard search filter

	Cohort Studies Controlled Before-After Studies Cross-Sectional Studies Epidemiologic Studies Observational Study	
Limits	Exclude Animal studies Exclude letters, editorials and letters Limit date to 2000 -Current	Standard search limits

Appendix D: Study flow diagram



Appendix E: Included studies

Francis N, Ridd MJ, Thomas-Jones E, Shepherd V, Butler CC, Hood K, Huang C, Addison K, Longo M, Marwick C, Wootton M. A randomised placebo-controlled trial of oral and topical antibiotics for children with clinically infected eczema in the community: the ChildRen with Eczema, Antibiotic Management (CREAM) study. Health Technology Assessment. 2016 Mar 1;20(19):1-84.

George SM, Karanovic S, Harrison DA, Rani A, Birnie AJ, Bath-Hextall FJ, Ravenscroft JC, Williams HC. Interventions to reduce Staphylococcus aureus in the management of eczema. Cochrane Database of Systematic Reviews. 2019(10).

Larsen FS, Simonsen L, MELgAARD A, Wendicke K, Henriksen AS. An efficient new formulation of fusidic acid and betamethasone 17-valerate (Fucicort® Lipid cream) for treatment of clinically infected atopic dermatitis. Acta dermato-venereologica. 2007 Jan 15;87(1):62-8.

Pratap DV, Philip M, Rao NT, Jerajani HR, Kumar SA, Kuruvila M, Moodahadu LS, Dhawan S. Evaluation of efficacy, safety, and tolerability of fixed dose combination (FDC) of halometasone 0.05% and fusidic acid 2% w/w topical cream versus FDC of betamethasone valerate 0.12% and neomycin sulphate 0.5% w/w topical cream in the treatment of infected eczematous dermatosis in Indian subjects: A randomized open-label comparative phase III multi-centric trial. Indian journal of dermatology. 2013 Mar;58(2):117.

Rist T, Parish LC, Capin LR, Sulica V, Bushnell WD, Cupo MA. A comparison of the efficacy and safety of mupirocin cream and cephalexin in the treatment of secondarily infected eczema. Clinical and Experimental Dermatology: Clinical dermatology. 2002 Jan;27(1):14-20.

Appendix F:Quality assessment of included studies

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

Study reference	**George et al. 2019**
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?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Yes
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes – no restrictions on date, sample size, or study quality and included outcomes are appropriate
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes - no restrictions on sources of information and reasonable efforts made to identify all relevant literature
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?	Yes
2.2 Were methods additional to database searching used to identify relevant reports?	Yes
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes – no restrictions on date, publication format or language
2.5 Were efforts made to minimise error in selection of studies?	Yes – independent screening performed by 2 reviewers and discrepancies resolved
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?	Yes – data extraction performed by 2 independent reviewers with discrepancies resolved and primary study authors were contacted to obtain missing data where possible
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes – in general sufficient information was available

3.3 Were all relevant study results collected for use in the synthesis?	Yes	
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes	
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes – risk of bias assessment performed by 2 independent reviewers and discrepancies resolved	
DOMAIN 4: SYNTHESIS AND FINDINGS - *Describe synthesis methods:*		
4.1 Did the synthesis include all studies that it should?	Yes – the NICE search did not find additional studies which would have been eligible	
4.2 Were all pre-defined analyses reported or departures explained?	Yes	
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes – meta-analysis performed for similar studies and narrative result reported for studies which did not provide sufficient data for meta-analysis	
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Yes – random effects model used for meta-analysis due to clinical heterogeneity	
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	No – sensitivity analysis based on methodological quality was planned, however no more than 4 studies were included in a meta-analysis and therefore this was not performed; a funnel plot analysis was planned but was not performed as fewer than 10 studies were pooled in any comparison	
4.6 Were biases in primary studies minimal or addressed in the synthesis?	No - bias was not explicitly addressed in the synthesis, however few included primary studies had high risk of bias in more than 1 domain	
PHASE 3: JUDGING RISK OF BIAS	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria	Low	Very clear eligibility criteria reported and these are reasonable
2. Concerns regarding methods used to identify and/or select studies	Low	Adequate search strategy used and used for a number of different databases; grey literature searches conducted and correspondence with trial authors
3. Concerns regarding methods used to collect data and appraise studies	Low	A pre-defined data extraction plan was specified and adhered to
4. Concerns regarding the synthesis and findings	Low	Risk of bias assessed and reported for each included study; reasons for exclusion are listed for excluded studies; results reported within meta-analysis where appropriate as well as narratively and narrative results reported where meta-analysis could not be performed
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?	Yes	

B. Was the relevance of identified studies to the review's research question appropriately considered?	Yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review: **LOW** Rationale for risk: Methods for identifying and interpreting primary studies was robust, analysis was clear and appropriate and information from primary studies, including risk of bias is comprehensively reported.	

Table 3: Overall risk of bias/quality assessment – RCTs (Cochrane Risk of Bias Tool 2.0)

Study reference	**Francis et al. 2016**
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 -** allocation sequence was randomly generated using computer; baseline imbalances in severity of eczema are likely due to chance based on description of methods followed for randomisation and allocation concealment
Domain 2a: 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	**Low** – participants and people delivering the intervention were not aware of the assigned intervention during the trial; no evidence of deviations from the intended intervention; appropriate intention to treat analysis used to determine the effect of assignment to intervention
Domain 2b: 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 -** participants and people delivering the intervention were not aware of the assigned intervention during the trial; adherence was relatively low with mean adherence 70.4% in the oral antibiotic group and 80.8% in the topical antibiotic, 80.8% (adherence to active treatment) but appropriate analysis used to estimate effect of adhering to the intervention (authors performed a CACE analysis showing very similar results to the intention to treat results, indicating that medication adherence did not significantly influence results)
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	**High -** potential attrition bias as loss to follow-up or withdrawal over 2 weeks/3 months varied across groups - oral antibiotics: 6%/22%, topical antibiotics - 16%/43%; no evidence that result was no biased by missing outcome data; missingness in the outcome may depend on its true value.
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** – method of measuring outcome appropriate (combination of subjective quality of life outcomes and objective outcomes); measurement was obtained from each group in the same way; outcome assessors did not know the intervention received.
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 –** a prespecified plan was followed for analysis and no evidence of selective data reporting
Overall risk-of-bias judgement	**Some concerns –** based on high risk of bias in missing outcome data domain
Study reference	**Larsen et al. 2007**
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 -** allocation sequence was random using a computer and concealed before assignment to intervention.
Domain 2a: 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 –** participants were not aware of their assigned intervention; although this was a double blind trial, there are some concerns as it was possible to distinguish between placebo and intervention topical cream, so it is possible that people delivering the intervention may have been able to distinguish the treatment being given. However, it is unlikely that participants were aware of the arm they were assigned to. There is no evidence of deviations from the intended intervention.
Domain 2b: 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** – there is no evidence that other co-interventions would have been sought by participants and that these would not be balanced across groups if they were; adherence to study medication was good and balanced across groups
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 –** data was available for nearly all participants randomised
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 –** appropriate methods used to collect data collected by the same methods for each group; there is a possibility that different outcome assessors were used for intervention and control groups, but there is no evidence to suggest this did occur or that bias has occurred due to this possibility; it is suggested that the outcome assessors were blinded although not explicitly stated.
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 –** the trial was analysed in accordance with a pre-specified plan with no evidence of data selection or selective reporting bias
Overall risk-of-bias judgement	**Low**
Study reference	**Pratap et al. 2013**
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 -** allocation sequence was random using a computer and concealed before assignment to intervention.
Domain 2a: 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	**High** – open label trial, with both participants and people delivering the intervention aware of the assigned intervention during the trial; there is no information to suggest whether there were deviations from the intended intervention
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention): Were participants / carers / people delivering the intervention aware of their assigned intervention during the trial? If yes, were important co-interventions balanced across intervention groups? Could failures in implementing the intervention have affected the outcome? Did study participants adhere to the assigned intervention regimen? If not, was an appropriate analysis used to estimate the effect of adhering to the intervention?	
Risk-of-bias judgement	**Some concerns –** participants were aware of their assigned intervention during the trial; there were very low numbers of withdrawal dur to non-compliance indicating that the outcome wasn't affected by lack of implementation; no information is reported about measuring for use of other interventions throughout the study period
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 –** there are low number of withdrawals and no evidence that the result was biased by any missing data
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	**High - o**utcome measurement was at different time points for people with chronic and acute eczema because these populations were given interventions for different lengths, but it is not explained why this was performed; no information is provided about whether the same outcome assessors were measuring each groups outcomes and outcome assessors were aware of the intervention received by participants
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	**Some concerns –** there is no information if a pre-specified plan was used for data analysis, however, no evidence of selective reporting bias
Overall risk-of-bias judgement	**High –** based on high risk of bias for possible deviations from the intended interventions and in measurement of the outcome as well as concerns about effect of adhering to the intervention and reporting of the results
Study reference	**Rist 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 -** allocation sequence was random using a computer and concealed before assignment to intervention.
Domain 2a: 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	**Low –** participants were not aware of their assigned intervention
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention): Were participants / carers / people delivering the intervention aware of their assigned intervention during the trial? If yes, were important co-interventions balanced across intervention groups? Could failures in implementing the intervention have affected the outcome? Did study participants adhere to the assigned intervention regimen? If not, was an appropriate analysis used to estimate the effect of adhering to the intervention?	
Risk-of-bias judgement	**Some concerns –** failures in implementing the intervention may have affected the outcome - 22 participants were excluded due to less than 80% compliance, however it is not clear if this was balanced across groups; however pre-protocol and intention to treat analysis both performed
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	**High** – there was a high attrition rate of 48% the reasons for withdrawal are reported and more participants in 1 arm withdrew due to reasons related to study drug (lack of efficacy or adverse events) therefore, missingness in the data could depend on its true value.
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** – measurement of outcome was appropriate and measurement was consistent across groups; no evidence of outcome assessors being aware of the intervention received.
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 –** no information on use of a pre-specified plan for data analysis, however, there is no evidence of reporting bias such as multiple outcome measures or time points being reported.
Overall risk-of-bias judgement	**Some concerns –** based on high risk of bias in missing outcome data, and some concerns on effect of adhering to the intervention, but low risk of bias in other domains.

Appendix G: GRADE profiles

G.1 Efficacy of antibiotics

G.1.1 Oral antibiotics

Table 4: GRADE profile – Oral antibiotics compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral antibiotic[1,2]	Placebo[2]	Relative (95% CI)	Absolute		
Number of people experiencing adverse events requiring withdrawal from treatment												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	2/52 (3.8%)	1/57 (1.8%)	RR 1.75 (0.22 to 13.73)	13 more per 1000 (from 14 fewer to 223 more)	⊕OOO VERY LOW	CRITICAL
Number of people in whom *Staphylococcus aureus* was isolated at end of treatment												
2[3]	randomised trials	serious[4]	serious[6]	no serious indirectness	very serious[5]	none	22/47 (46.8%)	29/51 (56.9%)	RR 0.70 (0.22 to 2.23)	171 fewer per 1000 (from 444 fewer to 699 more)	⊕OOO VERY LOW	IMPORTANT
Abbreviations: CI – confidence interval, RR – relative risk												

[1] Oral antibiotic either: flucloxacillin, 125 mg in 2.5 ml for children aged 3 months to 2 years or 250 mg in 5 ml for children aged 2 to 8 years, four times a day for 7 days or cefadroxil, 50 mg/kg/day in 2 equal doses for 14 days

[2] 70% of participants received topical corticosteroids (clobetasone butyrate 0.05% cream or ointment for use on trunk/limbs and/or hydrocortisone 1% cream or ointment for use on face, applied once a day for 14 days) and were encouraged to use emollients.

[3] George et al. 2019 (primary data from Weinberg et al. 1992 and Francis et al. 2016)

[4] Downgraded 1 level - systematic review authors noted high risk of bias from incomplete outcome data and baseline imbalance in severity and presence of *S. aureus* (Francis et al. 2016) and; unclear risk of bias in randomisation method, allocation concealment and blinding, and high risk of bias in incomplete outcome data and selective reporting (Weinberg et al. 1992)

[5] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

[6] Downgraded 1 level - heterogeneity > 50%

Table 5: GRADE profile – Oral flucloxacillin compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral flucloxacillin	Placebo	Relative (95% CI)	Absolute		
Change from baseline in IDQoL at end of treatment (flucloxacillin versus placebo) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	20	-	MD 0.11 higher (0.1 lower to 0.32 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change from baseline in IDQoL at 3 months (flucloxacillin versus placebo) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18	16	-	MD 0.21 lower (0.44 lower to 0.02 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change from baseline in CDLQI at end of treatment (flucloxacillin versus placebo) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	9	14	-	MD 0.43 higher (0.16 lower to 1.02 higher)	⊕⊕OO LOW	CRITICAL
Change from baseline in CDLQI at 3 months (flucloxacillin versus placebo) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6	8	-	MD 0.14 lower (0.97 lower to 0.69 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change from baseline in POEM at end of treatment (flucloxacillin versus placebo) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[6]	none	34	36	-	MD 1.52 higher (1.36 lower to 4.4 higher)	⊕⊕OO LOW	CRITICAL
Change from baseline in POEM at 3 months (flucloxacillin versus placebo) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28	25	-	MD 0.21 lower (3.12 lower to 2.7 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change from baseline in EASI at end of treatment (flucloxacillin versus placebo) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	34	-	MD 0.2 higher (0.12 lower to 0.52 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change from baseline in isolation rate of S. aureus at end of treatment (2 weeks) (Better indicated by lower values; percentage)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[7]	none	34	34	-	MD 14.5% lower (45.98% lower to 16.98% higher)	⊕⊕OO LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on SKIN at EOT (2 weeks) (resistance to Flucloxacillin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	0/18 (0%)	0/16 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on SKIN at EOT (2 weeks) (resistance to Erythromycin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[8]	none	1/18 (5.6%)	2/16 (12.5%)	RR 0.44 (0.04 to 4.45)	70 fewer per 1000 (from 120 fewer to 431 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on SKIN at EOT (2 weeks) (resistance to Fusidic acid))												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[8]	none	1/18 (5.6%)	5/16 (31.3%)	RR 0.18 (0.02 to 1.37)	256 fewer per 1000 (from 306 fewer to 116 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus in NOSE at EOT (2 weeks) (resistance to Flucloxacillin)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral flucloxacillin	Placebo	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	0/13 (0%)	0/9 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus in NOSE at EOT (2 weeks) (resistance to Erythromycin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[8]	none	1/13 (7.7%)	1/9 (11.1%)	RR 0.69 (0.05 to 9.68)	34 fewer per 1000 (from 106 fewer to 964 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus in NOSE at EOT (2 weeks) (resistance to Fusidic acid)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[8]	none	2/13 (15.4%)	4/9 (44.4%)	RR 0.35 (0.08 to 1.5)	289 fewer per 1000 (from 409 fewer to 222 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus in MOUTH at EOT (2 weeks) (resistance to Flucloxacillin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	0/4 (0%)	0/4 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus in MOUTH at EOT (2 weeks) (resistance Erythromycin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[8]	none	3/4 (75%)	0/4 (0%)	RR 7.00 (0.47 to 103.27)	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus in MOUTH at EOT (2 weeks) (resistance to Fusidic acid)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[8]	none	2/4 (50%)	1/4 (25%)	RR 2.00 (0.28 to 14.2)	250 more per 1000 (from 180 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus at 3 months (Better indicated by lower values; percentage)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[10]	none	26	25	-	MD 32.6% lower (65.92% lower to 0.72% higher)	⊕⊕OO LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on SKIN at 3 months (resistance to Flucloxacillin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[8]	none	1/8 (12.5%)	0/10 (0%)	RR 3.67 (0.17 to 79.54)	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on SKIN at 3 months (resistance to Erythromycin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[8]	none	1/8 (12.5%)	1/10 (10%)	RR 1.25 (0.09 to 17.02)	25 more per 1000 (from 91 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on SKIN at 3 months (resistance to Fusidic acid)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[8]	none	0/8 (0%)	2/10 (20%)	RR 0.24 (0.01 to 4.47)	152 fewer per 1000 (from 198 fewer to 694 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on NOSE at 3 months (resistance to Flucloxacillin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	0/11 (0%)	0/8 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on NOSE at 3 months (resistance to Erythromycin)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral flucloxacillin	Placebo	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	0/11 (0%)	0/8 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on NOSE at 3 months (resistance to Fusidic acid)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[8]	none	2/11 (18.2%)	1/8 (12.5%)	RR 1.45 (0.16 to 13.41)	56 more per 1000 (from 105 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on MOUTH at 3 months (resistance to Flucloxacillin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	0/5 (0%)	0/5 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on MOUTH at 3 months (resistance to Erythromycin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	0/5 (0%)	0/5 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on MOUTH at 3 months (resistance to Fusidic acid)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[8]	none	0/5 (0%)	3/5 (60%)	RR 0.14 (0.01 to 2.21)	516000 fewer per 1,000,000 (from 594000 fewer to 726000 more)	⊕OOO VERY LOW	CRITICAL

[1] Flucloxacillin: 125 mg in 2.5 ml for children aged 3 months to 2 years or 250 mg in 5 ml for children aged 2 to 8 years, four times a day for 7 days
[2] All participants received topical steroids (clobetasone butyrate 0.05% cream or ointment for use of trunk/limbs and/or hydrocortisone 1% cream or ointment for use on face, applied one a day for 14 days) and were encouraged to use emollients.
[3] George et al. 2019 (primary data from Francis et al. 2016)
[4] Downgraded 1 level - systematic review authors noted high risk of bias from incomplete outcome data and baseline imbalance in severity and presence of *S. Aureus* (Francis et al. 2016)
[5] Downgraded 1 level - at a minimal important difference of 0.99 , data are consistent with no meaningful difference or appreciable harm with oral flucloxacillin
[6] Downgraded 1 level - at a minimally important difference of 3.4 (published MID for POEM) data are consistent with no meaningful difference or appreciable harm with oral flucloxacillin
[7] Downgraded 1 level - at a minimal important difference of34.6%, data are consistent with no meaningful difference or appreciable harm with placebo
[8] Downgraded 2 levels – unable to assess imprecision as likely insufficient power to detect in addition to insufficient event rate
[9]
[10] Downgraded 1 level - at a minimal important difference of 28.05%, data are consistent with no meaningful difference or appreciable harm with placebo

Table 6: GRADE profile – Oral cefadroxil compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cefadroxil[1]	Placebo	Relative (95% CI)	Absolute		
Global outcome good or excellent at end of treatment												
1[2]	randomised trials	serious[3]	NA	serious[4]	serious[5]	none	10/12 (83.3%)	9/17 (52.9%)	RR 1.57 (0.94 to 2.63)	302 more per 1000 (from 32 fewer to 863 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cefadroxil[1]	Placebo	Relative (95% CI)	Absolute		
Number of people with erythema at end of treatment												
1[2]	randomised trials	serious[3]	NA	serious[4]	very serious[6]	none	5/13 (38.5%)	7/17 (41.2%)	RR 0.93 (0.38 to 2.28)	29 fewer per 1000 (from 255 fewer to 527 more)	⊕OOO VERY LOW	CRITICAL
Number of people with clinically apparent infection at end of treatment												
1[2]	randomised trials	serious[3]	NA	serious[4]	serious[7]	none	0/13 (0%)	9/15 (60%)	RR 0.06 (0.00 to 0.94)	564 fewer per 1000 (from 600 fewer to 36 fewer)	⊕OOO VERY LOW	CRITICAL
Number of withdrawals due to an adverse event												
1[2]	randomised trials	serious[3]	NA	serious[4]	serious[7]	none	1/13 (7.69%)	0/17 (0%)	RR 3.85 (0.17 to 87.7)	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval, NA – not applicable, RR – relative risk												

[1] Cefadroxil, 50 mg/kg/day in 2 equal doses for 14 days
[2] George et al. 2019 (primary data from Weinberg et al. 1992)
[3] Downgraded 1 level - systematic review authors noted unclear risk of bias in randomisation method, allocation concealment and blinding, and high risk of bias in incomplete outcome data and selective reporting
[4] Downgraded 1 level - 28/30 evaluable participants had clinically infected eczema
[5] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with an oral antibiotic
[6] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[7] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with placebo

G.1.2 Topical antibiotics

Table 7: GRADE profile – Topical antibiotic plus topical corticosteroid compared with topical corticosteroid

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic plus topical steroid[1]	Topical steroid[2]	Relative (95% CI)	Absolute		
No of patients in whom *Staphylococcus aureus* was isolated at end of treatment												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic plus topical steroid[1]	Topical steroid[2]	Relative (95% CI)	Absolute		
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	15/56 (26.8%)	20/61 (32.8%)	RR 0.80 (0.47 to 1.38)	66 fewer per 1000 (from 174 fewer to 125 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval, RR – relative risk												

[1] Topical fusidic acid 2% cream, 3 times a day for 7 days plus topical steroids (clobetasone butyrate 0.05% cream or ointment for use on trunk/limbs and/or hydrocortisone 1% cream or ointment for use on face, applied once a day for 14 days) and encouraged to use emollients; or, topical gentamicin and betamethasone valerate cream, applied 3 times a day for 22 days
[2] Topical steroids: placebo plus clobetasone butyrate 0.05% cream or ointment for use of trunk/limbs and/or hydrocortisone 1% cream or ointment for use on face, applied once a day for 14 days and encouraged to use emollients; or betamethasone valerate cream, applied 3 times a day for 22 days
[3] George et al. 2019 (primary data from Wachs et al.1976 and Francis et al. 2016)
[4] Downgraded 1 level - systematic review authors noted unclear risk of bias in most domains and high risk of bias from selective reporting (Wachs et al. 1976); and high risk of bias from incomplete outcome data and baseline imbalance in severity and presence of *S. aureus* (Francis et al. 2016)
[5] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 8: GRADE profile – Topical fusidic acid plus topical corticosteroid compared with placebo plus topical corticosteroid

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical fusidic acid plus topical steroid	Placebo plus topical steroid	Relative (95% CI)	Absolute		
Change from baseline in IDQoL at end of treatment (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22	20	-	MD 0.18 higher (0.04 lower to 0.4 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change from baseline in IDQoL at 3 months (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	16	-	MD 0.07 lower (0.31 lower to 0.17 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change from baseline in CDLQI at end of treatment (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	9	14	-	MD 0.7 higher (0.12 to 1.28 higher)	⊕⊕OO LOW	CRITICAL
Change from baseline in CDLQI at 3 months (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6	8	-	MD 0.13 lower (0.96 lower to 0.7 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change from baseline in POEM at end of treatment (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[6]	none	31	36	-	MD 1.49 higher (1.55 lower to 4.53 higher)	⊕⊕OO LOW	

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical fusidic acid plus topical steroid	Placebo plus topical steroid	Relative (95% CI)	Absolute		
Change from baseline in POEM at 3 months (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[7]	none	21	25	-	MD 1.13 lower (4.32 lower to 2.06 higher)	⊕⊕OO LOW	CRITICAL
Change from baseline in EASI at end of treatment (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31	34	-	MD 0.42 higher (0.09 to 0.75 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change from baseline in isolation rate (2 weeks) of S. aureus at end of treatment (Better indicated by lower values; percentage)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	31	34	-	MD 15.3% lower (48.43% lower to 17.83% higher)	⊕⊕OO LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on SKIN at end of treatment (2 weeks) (resistant to Flucloxacillin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	2/11 (18.2%)	0/16 (0%)	RR 7.08 (0.37 to 134.67)	-	⊕⊕OO LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on SKIN at end of treatment (2 weeks) (resistance to Erythromycin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	0/11 (0%)	2/16 (12.5%)	RR 0.28 (0.01 to 5.39)	90 fewer per 1000 (from 124 fewer to 549)	⊕⊕OO LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on SKIN at end of treatment (2 weeks) (resistance to Fusidic acid)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[9]	none	8/11 (72.7%)	5/16 (31.2%)	RR 2.33 (1.03 to 5.24)	416 more per 1000 (from 9 more to 1000 more)	⊕⊕OO LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on NOSE at end of treatment (2 weeks) (resistance to flucloxacillin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[9]	none	2/13 (15.4%)	0/9 (0%)	RR 3.57 (0.19 to 66.61)	-	⊕⊕OO LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on NOSE at end of treatment (2 weeks) (resistance to Erythromycin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[10]	none	1/13 (7.7%)	1/9 11.1%	RR 0.69 (0.05 to 68)	34 fewer per 1000 (from 106 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on NOSE at end of treatment (2 weeks) (resistance to Fusidic acid)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[10]	none	7/13 (53.8%)	4/9 (44.4%)	RR 1.21 (0.50 to 2.94)	93 more per 1000 (from 222 fewer to 862 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on MOUTH at end of treatment (2 weeks) (resistance to Erythromycin)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical fusidic acid plus topical steroid	Placebo plus topical steroid	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[10]	none	1/3 (33.3%)	0/4 (0%)	RR 3.75 (0.20 to 69.40)	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on MOUTH at end of treatment (2 weeks) (resistance to Flucloxacillin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[10]	none	1/3 (33.3%)	0/4 (0%)	RR 3.75 (0.20 to 69.40)	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on MOUTH at end of treatment (2 weeks) (resistance to Fusidic acid)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[10]	none	3/3 (100%)	1/4 25%	RR 2.92 (0.73 to 11.70)	480 more per 1000 (from 67 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus at 3 months (Better indicated by lower values; percentage)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[11]	none	21	25	-	MD 8.6% lower (45.44% lower to 28.24 higher)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on SKIN at 3 months (resistance to Flucloxacillin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[10]	none	1/8 (12.5%)	0/10 (0%)	RR 3.67 (0.17 to 79.54)	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on SKIN at 3 months (resistance to Erythromycin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[10]	none	1/8 (12.5%)	1/10 (10%)	RR 1.25 (0.09 to 17.02)	25 more per 1000 (from 91 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on SKIN at 3 months (resistance to Fusidic acid))												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[10]	none	2/8 (25%)	2/10 (20%)	RR 1.25 (0.22 to 7.02)	50 more per 1000 (from 156 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on NOSE at 3 months (resistance to Flucloxacillin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[11]	none	0/8 (0%)	0/8 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on NOSE at 3 months (resistance to Erythromycin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[10]	none	1/8 (12.5%)	0/8 (0%)	RR 3.00 (0.14 to 64.26)	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on NOSE at 3 months (resistance to Fusidic acid)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[10]	none	3/8 (37.5%)	1/8 (12.5%)	RR 3.00 (0.39 to 23.07)	250 more per 1000 (from 76 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical fusidic acid plus topical steroid	Placebo plus topical steroid	Relative (95% CI)	Absolute		
Change from baseline in isolation rate of S. aureus on MOUTH at 3 months (resistance to Flucloxacillin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[11]	none	0/1 (0%)	0/5 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on MOUTH at 3 months (resistance to Fusidic acid)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[10]	none	0/1 (0%)	3/5 (60%)	RR 0.43 (0.04 to 5.19)	342 fewer per 1000 (from 576 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Change from baseline in isolation rate of S. aureus on MOUTH at 3 months (resistance to Erythromycin)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[11]	none	0/1 (0%)	0/5 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
People reporting adverse events requiring withdrawal from treatment												
1[3]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[10]	none	5/37 (13.5%)	1/40 (2.5%)	RR 5.41 (0.66 to 44.14)	110 more per 1000 (from 8 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Mean value of composite rating scale at end of treatment (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31	34	-	SMD 0.42 higher (0.07 lower to 0.91 higher)	⊕⊕⊕O MODERATE	CRITICAL

[1] Topical fusidic acid 2% cream, 3 times a day for 7 days plus topical steroids (clobetasone butyrate 0.05% cream or ointment for use of trunk/limbs and/or hydrocortisone 1% cream or ointment for use on face, applied one a day for 14 days) and encouraged to use emollients
[2] Topical steroids (clobetasone butyrate 0.05% cream or ointment for use of trunk/limbs and/or hydrocortisone 1% cream or ointment for use on face, applied one a day for 14 days) and encouraged to use emollients
[3] George et al. 2019 (primary data from Francis et al. 2016)
[4] Downgraded 1 level - systematic review authors noted high risk of bias from incomplete outcome data and baseline imbalance in severity and presence of S. aureus (Francis et al. 2016)
[5] Downgraded 1 level - at a minimal important difference of 0.99, data are consistent with no meaningful difference or appreciable harm with topical antibiotic
[6] Downgraded 1 level - at a minimally important difference of 3.4 (published MID for POEM) data are consistent with no meaningful difference or appreciable harm with topical fusidic acid
[7] Downgraded 1 level - at a minimally important difference of 3.4 (published MID for POEM) data are consistent with no meaningful difference or appreciable harm with placebo plus topical steroid
[8] Downgraded 1 level - at a minimal important difference of 34.6%, data are consistent with no meaningful difference or appreciable harm with placebo plus topical steroid
[9] Downgraded 1 levels - at a default minimal important difference of 25% relative risk increase the effect estimate is consistent with no appreciable benefit.
[10] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[11] Downgraded 2 levels – unable to assess imprecision as likely insufficient power to detect in addition to insufficient event rate

Table 9: GRADE profile – Topical gentamicin plus topical corticosteroid compared with topical corticosteroid

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical gentamicin plus topical steroid[1]	Topical steroid[2]	Relative (95% CI)	Absolute		
Global outcome of improvement of symptoms or signs (physician or patient) good or excellent at end of treatment												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	23/25 (92.0%)	20/27 (74.1%)	RR 1.24 (0.97 to 1.60)	178 more per 1000 (from 22 fewer to 444 more)	⊕⊕OO LOW	CRITICAL
Number of patients in whom S. aureus was isolated at end of treatment												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[5]	none	4/25 (16%)	4/27 (14.8%)	RR 1.08 (0.30 to 3.86)	12 more per 1000 (from 104 fewer to 424 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval, NA – not applicable, RR – relative risk												

[1] Topical gentamicin and betamethasone valerate cream, applied 3 times a day for 22 days
[2] Topical betamethasone cream applied 3 times a day for 22 days
[3] George et al. 2019 (primary data from Wachs et al. 1976)
[4] Downgraded 1 level - systematic review authors noted unclear risk of bias in most domains and high risk of bias from selective reporting
[5] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with topical gentamicin plus topical steroid
[6] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

G.1.3 Intranasal antibiotics with bleach bath

Table 10: GRADE profile – Topical mupirocin plus bleach bath compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical mupirocin plus bleach bath[1]	Placebo[2]	Relative (95% CI)	Absolute		
Change from baseline in EASI at 1 month (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	N= 11	N= 14	-	MD 7.9 lower with topical mupirocin (-14.22 to -1.58 lower)	⊕⊕OO LOW	CRITICAL
Change from baseline in EASI at 3 months (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical mupirocin plus bleach bath[1]	Placebo[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[6]	none	N= 9	N= 13	-	MD 12.1 lower with topical mupirocin (-20.18 to -4.02 lower)	⊕⊕OO LOW	CRITICAL
Number of patients with a reduction in IGA at 3 months												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[7]	none	6/9 (66.7%)	2/13 (15.4%)	RR 4.33 (1.12 to 16.82)	512 more per 1000 (from 18 more to 1000 more)	⊕⊕OO LOW	CRITICAL
Number of patients in whom *Staphylococcus aureus* was isolated at 1 month												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[8]	none	6/11 (54.5%)	10/13 (76.9%)	RR 0.71 (0.38 to 1.31)	223 fewer per 1000 (from 477 fewer to 238 more)	⊕OOO VERY LOW	CRITICAL
Number of patients in whom *Staphylococcus aureus* was isolated at 3 months												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[9]	none	7/8 (87.5%)	10/13 (76.9%)	RR 1.14 (0.77 to 1.69)	108 more per 1000 (from 177 fewer to 531 more)	⊕⊕OO LOW	CRITICAL
Number of patients in whom MRSA was isolated at 1 month												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[8]	none	1/11 (9.1%)	0/13 (0%)	RR 3.50 (0.16 to 78.19)	-	⊕OOO VERY LOW	CRITICAL
Number of patients in whom MRSA was isolated at 3 months												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[8]	none	1/8 (12.5%)	1/13 (7.7%)	RR 1.63 (0.12 to 22.5)	48 more per 1000 (from 68 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Withdrawals due to adverse events												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[10]	none	0/11	0/13	-	-	⊕⊕OO LOW	CRITICAL
Minor patient reported adverse events												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[8]	none	1/11 (9.1%)	0/11	RR 3.00 (0.14 to 66.5)	-	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval, MRSA – methicillin-resistant *Staphylococcus aureus*, NA – not applicable, RR – relative risk, EASI – Eczema Area and Severity Index, MD – mean difference, IGA – Investigator Global Assessment

[1] Mupirocin ointment applied intranasally twice a day for 5 consecutive days of each month, plus 0.5 cup of 6% bleach in a full bathtub (40 gallons) of water (final concentration bleach 0.005%) for bathing in 5 to 10 minutes twice weekly

[2] Petrolatum applied intranasally twice a day for 5 consecutive days of each month, plus water added to a full bath (placebo) for bathing in 5 to 10 minutes twice weekly

[3] George et al. 2019 (primary data from Huang et al. 2009)

[4] Downgraded 1 level - systematic review authors note unclear risk of bias in blinding of outcome assessment and high risk of bias in blinding of participants, incomplete outcome data, selective reporting and imbalance in eczema severity between groups as baseline

[5] Downgraded 1 level - at a minimal important difference of 2.995, data are consistent with no meaningful difference or appreciable benefit with topical antibiotic plus bleach bath

[6] Downgraded 1 level - at a minimal important difference of 2.885, data are consistent with no meaningful difference or appreciable benefit with topical antibiotic plus bleach bath

[7]Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with topical mupirocin plus bleach bath
[8] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[9] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with topical mupirocin plus bleach bath
[10] Downgraded 2 levels – unable to assess imprecision as likely insufficient power to detect in addition to insufficient event rate

G.2 Efficacy of antibiotic and steroid combination

G.2.1 Topical antibiotic plus topical steroid

Table 11: GRADE profile – Topical fusidic acid plus topical corticosteroid compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fusidic acid plus steroid[1]**	**Placebo[2]**	**Relative (95% CI)**	**Absolute**		
Total severity score (mean percentage reduction from baseline to end of treatment [14 days])												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	82.7% N= 275	33.0% N= 90	Estimated treatment difference 48.3% (41.0% to 55.7%), p < 0.001	-	⊕⊕⊕O MODERATE	CRITICAL
Number of responders (people with marked improvement or complete clearance) at end of treatment (14 days)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	230/275 (83.6%)	28/90 (31.1%)	RR 2.69 (1.97 to 3.67)	526 more per 1000 (from 302 more to 831 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Number of people compliant with study treatment												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	239/275 (86.9%)	78/90 (86.7%)	RR 1.00 (0.91 to 1.10)	0 fewer per 1000 (from 78 fewer to 87 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Number of *Staphylococcus aureus* isolates resistant to fusidic acid at the end of treatment (14 days) in people infected with susceptive isolates at baseline (all strains susceptible at baseline)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	7/303 (2.3%)	1/54 (1.9%)	RR 1.25 (0.16 to 9.94)	5 more per 1000 (from 16 fewer to 166 more)	⊕⊕OO LOW	CRITICAL
Number with successful biological response (baseline pathogen eradicated or no visible target lesion) at end of treatment (14 days)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	241/275 (87.6%)	23/90 (25.6%)	RR 3.43 (2.40 to 4.89)	621 more per 1000 (from 358 more to 994 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Number reporting adverse events												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fusidic acid plus steroid[1]	Placebo[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[6]	none	37/274 (13.5%)	19/88 (21.6%)	RR 0.63 (0.38 to 1.03)	80 fewer per 1000 (from 134 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
Number reporting adverse drug reactions												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	7/274 (2.6%)	12/88 (13.6%)	RR 0.19 (0.08 to 0.46)	110 fewer per 1000 (from 125 fewer to 74 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Abbreviations: CI – confidence interval, NA – not applicable, RR – relative risk												

[1] Fusidic acid (20 mg/g) and betamethasone 17-valerate 91 mg/g) in a lipid cream (Fucicort® Lipid cream, LEO Pharma, Ballerup, Denmark), applied twice a day for 14 days
[2] Lipid cream vehicle, applied twice a day for 14 days
[3] Larsen et al. 2007
[4] Downgraded 1 level - not assessable
[5] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with placebo

G.3 Efficacy of antiseptics

G.3.1 Antiseptic emollient

Table 12: GRADE profile – Triclosan and benzalkonium chloride compared with non-antimicrobial emollient

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oilatum Plus[1, 2]	Oilatum[2, 3]			
Global degree of improvement in symptoms and/or signs											
1[4]	randomised trials	very serious[5]	NA	serious[6]	serious[7]	none	N unknown[8]	N unknown[8]	"No statistically significant difference between the treatment groups"	⊕OOO VERY LOW	CRITICAL
Number of severe adverse events requiring withdrawal from treatment											
1[4]	randomised trials	very serious[5]	NA	serious[6]	serious[7]	none	1/ unknown[8]	1/ unknown[8]	1 participant in each group withdrew from treatment due to adverse event	⊕OOO VERY LOW	CRITICAL
Minor patient-reported adverse events											

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oilatum Plus[1, 2]	Oilatum[2, 3]			
1[4]	randomised trials	very serious[5]	NA	serious[6]	serious[7]	none	3/ unknown[8]	5/ unknown[8]	3 participants in oilatum plus and 5 in oilatum group reported adverse events	⊕OOO VERY LOW	CRITICAL
Abbreviations: NA – not applicable											

[1] Emollient plus triclosan and benzalkonium chloride
[2] 15 mL of emollient or emollient plus antiseptic used in an 8-inch bath of water, for soak for 10 to 15 minutes once a day for 4 weeks
[3] Emollient only
[4] George et al. 2019 (primary data from Harper et al. 1995)
[5] Downgraded 2 levels – systematic review authors report unclear risk of bias in allocation concealment, blinding and attrition bias; high risk of bias from incomplete outcome reporting including lack of statistical data and no baseline data
[6] Downgraded 1 level – population included people with eczema with recurrent infection, and/or frequent exacerbations – unclear how many had infection
[7] Downgraded 1 level – not assessable
[8] Total number of participants in both groups: 30 randomised, 26 evaluable

G.4 Choice of antibiotic

G.4.1 Topical antibiotic

Table 13: GRADE profile – Fusidic acid plus topical corticosteroid compared with neomycin plus topical corticosteroid

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fusidic acid and halometasone cream[1]	Neomycin and betamethasone cream[2]	Relative (95% CI)	Absolute		
EASI score (day 5 or 10) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	N= 70	N= 72	-	MD 0.1 lower with fusidic acid and halometasone (0.66 lower to 0.46 higher)	⊕⊕⊕O MODERATE	CRITICAL
EASI score (day 10 or 20) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	N= 70	N= 72	-	MD 0.07 lower with fusidic acid and halometasone (0.51 lower to 0.37 higher)	⊕⊕⊕O MODERATE	CRITICAL
EASI score (day 20 or 30) (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fusidic acid and halometasone cream[1]	Neomycin and betamethasone cream[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	N= 70	N= 72	-	MD 0.22 lower with fusidic acid and halometasone (0.58 lower to 0.14 higher)	⊕⊕⊕O MODERATE	CRITICAL
Number of people with positive bacterial culture at day 10												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	16/62 (25.8%)	38/67 (56.7%)	RR 0.46 (0.28 to 0.73)	306 fewer per 1000 (from 153 fewer to 408 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Number of people with positive bacterial culture at day 20 or 30												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	10/62 (16.1%)	23/67 (34.3%)	RR 0.47 (0.24 to 0.91)	182 fewer per 1000 (from 261 fewer to 31 fewer)	⊕⊕OO LOW	CRITICAL
IGA score (day 5 or 10) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	N= 70	N= 72	-	MD 0.08 lower with fusidic acid and halometasone (0.32 lower to 0.16 higher)	⊕⊕⊕O MODERATE	CRITICAL
IGA score (day 10 or 20) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	N= 70	N= 72	-	MD 0.07 lower with fusidic acid and halometasone (0.3 lower to 0.16 higher)	⊕⊕⊕O MODERATE	CRITICAL
IGA score (day 20 or 30) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	N= 70	N= 72	-	MD 0.1 lower with fusidic acid and halometasone (0.35 lower to 0.15 higher)	⊕⊕⊕O MODERATE	CRITICAL
Pruritic severity score (day 5 or 10) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[6]	none	N= 70	N= 72	-	MD 0.02 higher with fusidic acid and halometasone NICE analysis (CI not calculable)	⊕⊕OO LOW	CRITICAL
Pruritic severity score (day 10 or 20) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[6]	none	N= 70	N= 72	-	MD 0.13 higher with fusidic acid and halometasone	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fusidic acid and halometasone cream[1]	Neomycin and betamethasone cream[2]	Relative (95% CI)	Absolute		
										NICE analysis (CI not calculable)		
Pruritic severity score (day 20 or 30) (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[6]	none	N= 70	N= 72	-	MD 0.07 lower with fusidic acid and halometasone NICE analysis (CI not calculable)	⊕⊕OO LOW	CRITICAL
Number of people achieving grade 1 or mild pruritus at end of therapy												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[7]	none	24/77 (31.2%)	27/75 (36%)	RR 0.87 (0.55 to 1.36)	47 fewer per 1000 (from 162 fewer to 130 more)	⊕OOO VERY LOW	CRITICAL
Number of people relieved of itching at end of treatment												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[8]	none	37/77 (48.1%)	34/75 (45.3%)	RR 1.06 (0.75 to 1.49)	27 more per 1000 (from 113 fewer to 222 more)	⊕⊕OO LOW	CRITICAL
Number of people with mild to moderately severe eczema achieving early symptomatic relief at day 10												
1[3]	randomised trials	no serious risk of bias[4]	NA	no serious indirectness	serious[8]	none	41/77 (53.2%)	35/75 (46.7%)	RR 1.14 (0.83 to 1.57)	65 more per 1000 (from 79 fewer to 266 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of people achieving cure at day 20 or 30												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[8]	none	38/70 (54.3%)	36/72 (50.0%)	RR 1.09 (0.79 to 1.49)	45 more per 1000 (from 105 fewer to 245 more)	⊕⊕OO LOW	CRITICAL
Number of people improved at day 20 or 30												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[7]	none	28/70 (40%)	32/72 (44.4%)	RR 0.90 (0.61 to 1.32)	44 fewer per 1000 (from 173 fewer to 142 more)	⊕OOO VERY LOW	CRITICAL
Number of people with treatment failure at day 20 or 30												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[7]	none	4/70 (5.7%)	4/72 (5.6%)	RR 1.03 (0.27 to 3.95)	2 more per 1000 (from 41 fewer to 164 more)	⊕OOO VERY LOW	CRITICAL
Number of people with adverse events[9]												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[7]	none	3/77 (3.9%)	2/75 (2.7%)	RR 1.46 (0.25 to 8.50)	12 more per 1000 (from 20 fewer to 200 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval, EASI – Eczema Area and Severity Index, NA – not applicable, MD – mean difference, RR – relative risk, IGA – investigator global assessment												

[1] Fusidic acid (2%) and halometasone (0.05%) cream applied twice a day without any occlusive bandage to the eczematous skin, using enough to cover the entire affected area lightly; people with acute eczema were treated for 20 days, people with chronic eczema were treated for 30 days
[2] Neomycin sulfate (0.5%) and betamethasone (0.12%) cream applied twice daily without any occlusive bandage to the eczematous skin, using enough to cover the entire affected area lightly; people with acute eczema were treated for 20 days, people with chronic eczema were treated for 30 days
[3] Pratap et al. 2013
[4] Downgraded 1 level - open-label trial with no attempt to blind participants or outcome assessors; study funded by pharmaceutical company which produces fusidic acid and halometasone cream
[5] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with neomycin and betamethasone cream
[6] Downgraded 1 level - not assessable
[7] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[8] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with fusidic acid and halometasone cream
[9] Adverse events include hypopigmentation and dissemination in fusidic acid and halometasone cream group and ulcers and autosensitisation in neomycin and betamethasone cream group

G.5 Route of administration

G.5.1 Oral antibiotic compared with topical antibiotic

Table 14: GRADE profile – Oral flucloxacillin compared with topical fusidic acid: clinical outcomes

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral flucloxacillin[1, 2]	Topical fusidic acid[2, 3]	Relative (95% CI)	Absolute		
POEM score at 2 weeks (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[6]	none	N= 34	N= 31	-	MD 1.05 lower (4.33 lower to 2.23 higher)	⊕⊕OO LOW	CRITICAL
POEM score at 4 weeks (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[6]	none	N= 33	N= 30	-	MD 1.17 lower (4.54 lower to 2.2 higher)	⊕⊕OO LOW	CRITICAL
POEM score at 3 months (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	no serious imprecision	none	N= 28	N= 21	-	MD 0 higher (3.37 lower to 3.37 higher)	⊕⊕⊕O MODERATE	CRITICAL
EASI score at 2 weeks (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[7]	none	N= 34	N= 31	-	MD 1.82 lower (4.15 lower to 0.51 higher)	⊕⊕OO LOW	CRITICAL
EASI score at 4 weeks (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[8]	none	N= 33	N= 30	-	MD 1.75 lower (4.53 lower to 1.03 higher)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral flucloxacillin[1, 2]	Topical fusidic acid [2, 3]	Relative (95% CI)	Absolute		
DFI score at 2 weeks (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[9]	none	N= 34	N= 31	-	MD 1.15 lower (3.55 lower to 1.25 higher)	⊕⊕OO LOW	CRITICAL
DFI score at 4 weeks (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[10]	none	N= 33	N= 30	-	MD 0.71 lower (3.04 lower to 1.62 higher)	⊕⊕OO LOW	CRITICAL
DFI score at 3 months (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[11]	none	N= 25	N= 20	-	MD 0.64 lower (3.61 lower to 2.33 higher)	⊕⊕OO LOW	CRITICAL
IDQoL score at 2 weeks (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[12]	none	N= 25	N= 22	-	MD 0.72 lower (2.52 lower to 1.08 higher)	⊕⊕OO LOW	CRITICAL
IDQoL score at 4 weeks (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[13]	none	N= 24	N= 22	-	MD 0.55 lower (2.34 lower to 1.24 higher)	⊕⊕OO LOW	CRITICAL
IDQoL score at 3 months (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[14]	none	N= 18	N= 15	-	MD 0.66 lower (2.95 lower to 1.63 higher)	⊕⊕OO LOW	CRITICAL
CDLQI score at 2 weeks (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[15]	none	N= 9	N= 9	-	MD 1.81 lower (6.35 lower to 2.73 higher)	⊕⊕OO LOW	CRITICAL
CDLQI score at 4 weeks (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[816]	none	N= 9	N= 8	-	MD 1.32 higher (2.17 lower to 4.81 higher)	⊕OOO VERY LOW	CRITICAL
CDLQI score at 3 months (Better indicated by lower values)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[17]	none	N= 6	N= 6	-	MD 0.96 higher (5.56 lower to 7.48 higher)	⊕OOO VERY LOW	CRITICAL
Number with *Staphylococcus aureus* on the skin at 2 weeks												
1	randomised trials	serious[5]	NA	no serious indirectness	serious[18]	none	18/34 (52.9%)	11/31 (35.5%)	RR 1.49 (0.84 to 2.64)	174 more per 1000 (from 57 fewer to 582 more)	⊕⊕OO LOW	CRITICAL
Number with *Staphylococcus aureus* on the skin at 3 months												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[19]	none	8/26 (30.8%)	8/21 (38.1%)	RR 0.81 (0.37 to 1.79)	72 fewer per 1000 (from 240 fewer to 301 more)	⊕OOO VERY LOW	CRITICAL
Number with nausea (within 2 weeks from beginning of treatment)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral flucloxacillin[1, 2]	Topical fusidic acid[2, 3]	Relative (95% CI)	Absolute		
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[19]	none	2/33 (6.1%)	1/29 (3.4%)	RR 1.76 (0.17 to 18.39)	26 more per 1000 (from 29 fewer to 600 more)	⊕OOO VERY LOW	CRITICAL
Number with vomiting (within 2 weeks from beginning of treatment)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[19]	none	4/33 (12.1%)	2/29 (6.9%)	RR 1.76 (0.35 to 8.90)	52 more per 1000 (from 45 fewer to 545 more)	⊕OOO VERY LOW	CRITICAL
Number with diarrhoea (within 2 weeks from beginning of treatment)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[19]	none	5/33 (15.2%)	5/29 (17.2%)	RR 0.88 (0.28 to 2.73)	21 fewer per 1000 (from 124 fewer to 298 more)	⊕OOO VERY LOW	CRITICAL
Number with tummy pain (within 2 weeks from beginning of treatment)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[19]	none	3/33 (9.1%)	3/29 (10.3%)	RR 0.88 (0.19 to 4.02)	12 fewer per 1000 (from 84 fewer to 312 more)	⊕OOO VERY LOW	CRITICAL
Number with joint pains (within 2 weeks from beginning of treatment)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[19]	none	1/33 (3%)	2/29 (6.9%)	RR 0.44 (0.04 to 4.60)	39 fewer per 1000 (from 66 fewer to 248 more)	⊕OOO VERY LOW	CRITICAL
Number with new rash (within 2 weeks from beginning of treatment)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[19]	none	4/33 (12.1%)	5/29 (17.2%)	RR 0.7 (0.21 to 2.37)	52 fewer per 1000 (from 136 fewer to 236 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval, POEM – Patient Orientated Eczema Measure, NA – not applicable, MD – mean difference, EASI – Eczema Area and Severity Index, DFI – Dermatitis Family Impact, IDQoL – Infants' Dermatitis Quality of Life, CDLQI – Children's Dermatology Life Quality Index, RR – relative risk

[1] Flucloxacillin suspension, 250 mg/5 ml, 2.5 ml 4 times a day (children aged 3 months to 2 years) or 5 ml 4 times a day (children aged > 2 years to < 8 years)
[2] All participants received topical steroids (clobetasone butyrate 0.05% cream or ointment for use of trunk/limbs and/or hydrocortisone 1% cream or ointment for use on face, applied once a day for 14 days) and were encouraged to use emollients.
[3] Fusidic acid 2% cream applied to affected area(s) 3 times a day for 7 days
[4] Francis et al. 2016
[5] Downgraded 1 level - baseline imbalance in severity (mean POEM score: oral antibiotic group 14.62, topical antibiotic group 16.90) and potential attrition bias (loss to follow-up or withdrawal over 2 weeks/3 months: oral antibiotic group 6%/22%, topical antibiotic group 16%/43%)
[6] Downgraded 1 level - at a minimally important difference of 3.4 (published MID for POEM) data are consistent with no meaningful difference or appreciable harm with topical antibiotic
[7] Downgraded 1 level - at a minimal important difference of2.825, data are consistent with no meaningful difference or appreciable harm with topical antibiotic
[8] Downgraded 1 level - at a minimal important difference of 3.44, data are consistent with no meaningful difference or appreciable harm with topical antibiotic
[9] Downgraded 1 level - at a minimal important difference of 2.68, data are consistent with no meaningful difference or appreciable harm with topical antibiotic
[10] Downgraded 1 level - at a minimal important difference of 2.12, data are consistent with no meaningful difference or appreciable harm with topical antibiotic
[11] Downgraded 1 level - at a minimal important difference of 2.76, data are consistent with no meaningful difference or appreciable harm with topical antibiotic
[12] Downgraded 1 level - at a minimal important difference of 1.50, data are consistent with no meaningful difference or appreciable harm with topical antibiotic

[13] Downgraded 1 level - at a minimal important difference of 1.48, data are consistent with no meaningful difference or appreciable harm with topical antibiotic
[14] Downgraded 1 level - at a minimal important difference of 1.75, data are consistent with no meaningful difference or appreciable harm with topical antibiotic
[15] Downgraded 1 level - at a minimal important difference of 3.13, data are consistent with no meaningful difference or appreciable harm with topical antibiotic
[16] Downgraded 2 levels - at a minimal important difference of 1.11, data are consistent with no meaningful difference, appreciable benefit or appreciable harm[17]Downgraded 2 levels - at a minimal important difference of 2.31, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[18] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with oral antibiotics
[19] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 15: GRADE profile – Oral flucloxacillin compared with topical fusidic acid: resistance outcomes

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral flucloxacillin[1, 2]	Topical fusidic acid[2, 3]	Relative (95% CI)	Absolute		
Number with *Staphylococcus aureus* (from skin) resistant to flucloxacillin at 2 weeks												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[6]	none	0/18 (0%)	2/11 (18.2%)	RR 0.13 (0.01 to 2.41)	158 fewer per 1000 (from 180 fewer to 256 more)	⊕OOO VERY LOW	CRITICAL
Number with *Staphylococcus aureus* (from skin) resistant to flucloxacillin at 3 months												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[6]	none	1/8 (12.5%)	1/8 (12.5%)	RR 1.00 (0.07 to 13.37)	0 fewer per 1000 (from 116 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Number with *Staphylococcus aureus* (from skin) resistant to erythromycin at 2 weeks												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[6]	none	1/18 (5.6%)	0/11 (0%)	RR 1.89 (0.08 to 42.82)	-	⊕OOO VERY LOW	CRITICAL
Number with *Staphylococcus aureus* (from skin) resistant to erythromycin at 3 months												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[6]	none	1/8 (12.5%)	1/8 (12.5%)	RR 1.00 (0.07 to 13.37)	0 fewer per 1000 (from 116 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Number with *Staphylococcus aureus* (from skin) resistant to fusidic acid at 2 weeks												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	no serious imprecision	none	1/18 (5.6%)	8/11 (72.7%)	RR 8.00 (1.19 to 53.67)	669 fewer per 1000 (from 342 fewer to 720 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Number with *Staphylococcus aureus* (from skin) resistant to fusidic acid at 3 months												
1[4]	randomised trials	serious[4]	NA	no serious indirectness	very serious[6]	none	0/8 (0%)	2/8 (25%)	RR 0.20 (0.01 to 3.61)	200 fewer per 1000 (from 248 fewer to 652 more)	⊕OOO VERY LOW	CRITICAL
Number with *Staphylococcus aureus* (from nose) resistant to flucloxacillin at 2 weeks												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral flucloxacillin[1, 2]	Topical fusidic acid[2, 3]	Relative (95% CI)	Absolute		
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[6]	none	0/13 (0%)	2/13 (15.4%)	RR 0.20 (0.01 to 3.8)	123 fewer per 1000 (from 152 fewer to 431 more)	⊕OOO VERY LOW	CRITICAL
Number with *Staphylococcus aureus* (from nose) resistant to flucloxacillin at 3 months												
1[4]	randomised trials	serious[4]	NA	no serious indirectness	serious[7]	none	0/11 (0%)	0/8 (0%)	-	-	⊕⊕OO LOW	CRITICAL
Number with *Staphylococcus aureus* (from nose) resistant to erythromycin at 2 weeks												
1[4]	randomised trials	serious[4]	NA	no serious indirectness	very serious[6]	none	1/13 (7.7%)	1/13 (7.7%)	RR 1.00 (0.07 to 14.34)	0 fewer per 1000 (from 72 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Number with *Staphylococcus aureus* (from nose) resistant to erythromycin at 3 months												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[6]	none	0/11 (0%)	1/8 (12.5%)	RR 0.25 (0.01 to 5.45)	94 fewer per 1000 (from 124 fewer to 556 more)	⊕OOO VERY LOW	CRITICAL
Number with *Staphylococcus aureus* (from nose) resistant to fusidic acid at 2 weeks												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[8]	none	2/13 (15.4%)	7/13 (53.8%)	RR 0.29 (0.07 to 1.13)	382 fewer per 1000 (from 501 fewer to 70 more)	⊕⊕OO LOW	CRITICAL
Number with *Staphylococcus aureus* (from nose) resistant to fusidic acid at 3 months												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[6]	none	2/11 (18.2%)	3/8 (37.5%)	RR 0.48 (0.1 to 2.26)	195 fewer per 1000 (from 338 fewer to 472 more)	⊕OOO VERY LOW	CRITICAL
Number with *Staphylococcus aureus* (from mouth) resistant to flucloxacillin at 2 weeks												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[6]	none	0/4 (0%)	1/3 (33.3%)	RR 0.27 (0.01 to 4.93)	243 fewer per 1000 (from 330 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Number with *Staphylococcus aureus* (from mouth) resistant to flucloxacillin at 3 months												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[7]	none	0/5 (0%)	0/1 (0%)	-	-	⊕⊕OO LOW	CRITICAL
Number with *Staphylococcus aureus* (from mouth) resistant to erythromycin at 2 weeks												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[6]	none	3/4 (75%)	1/3 (33.3%)	RR 2.25 (0.41 to 12.28)	417 more per 1000 (from 197 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Number with *Staphylococcus aureus* (from mouth) resistant to erythromycin at 3 months												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[7]	none	0/5 (0%)	0/1 (0%)	-	-	⊕⊕OO LOW	CRITICAL
Number with *Staphylococcus aureus* (from mouth) resistant to fusidic acid at 2 weeks												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral flucloxacillin[1, 2]	Topical fusidic acid[2, 3]	Relative (95% CI)	Absolute		
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[6]	none	2/4 (50%)	3/3 (100%)	RR 0.57 (0.22 to 1.48)	430 fewer per 1000 (from 780 fewer to 480 more)	⊕OOO VERY LOW	CRITICAL
Number with *Staphylococcus aureus* (from mouth) resistant to fusidic acid at 3 months												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[7]	none	0/5 (0%)	0/1 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval, NA – not applicable, RR – relative risk												

[1] Flucloxacillin suspension, 250 mg/5 ml, 2.5 ml 4 times a day (children aged 3 months to 2 years) or 5 ml 4 times a day (children aged > 2 years to < 8 years)
[2] All participants received topical steroids (clobetasone butyrate 0.05% cream or ointment for use of trunk/limbs and/or hydrocortisone 1% cream or ointment for use on face, applied once a day for 14 days) and were encouraged to use emollients
[3] Fusidic acid 2% cream applied to affected area(s) 3 times a day for 7 days
[4] Francis et al. 2016
[5] Downgraded 1 level - baseline imbalance in severity (mean POEM score: oral antibiotic group 14.62, topical antibiotic group 16.90) and potential attrition bias (loss to follow-up or withdrawal over 2 weeks/3 months: oral antibiotic group 6%/22%, topical antibiotic group 16%/43%)
[6] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[7] Downgraded 1 level - small sample size (imprecision not assessable based on relative risk increase [RRI]/reduction [RRR] due to 0 events in each arm)
[8] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with topical antibiotics

Table 16: GRADE profile – Oral flucloxacillin compared with topical fusidic acid: healthcare utilisation outcomes

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral flucloxacillin[1, 2]	Topical fusidic acid[2,3]	Relative (95% CI)	Absolute		
Number of people with 1 or more healthcare consultations (within 4 weeks from beginning of treatment) - GP consultations[4]												
1[5]	randomised trials	serious[6]	NA	no serious indirectness	very serious[7]	none	10/33 (30.3%)	9/30 (30%)	RR 1.01 (0.48 to 2.14)	3 more per 1000 (from 156 fewer to 342 more)	⊕OOO VERY LOW	CRITICAL
Number of people with 1 or more healthcare consultations (in weeks 5 to 12 from beginning of treatment) - GP consultations[4]												
1[5]	randomised trials	serious[6]	NA	no serious indirectness	serious[8]	none	17/26 (65.4%)	10/21 (47.6%)	RR 1.37 (0.81 to 2.33)	176 more per 1000 (from 90 fewer to 633 more)	⊕⊕OO LOW	CRITICAL
Number of people with 1 or more healthcare consultations (within 4 weeks from beginning of treatment) - nurse consultations												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral flucloxacillin[1, 2]	Topical fusidic acid[2,3]	Relative (95% CI)	Absolute		
1[5]	randomised trials	serious[6]	NA	no serious indirectness	very serious[7]	none	4/33 (12.1%)	3/30 (10%)	RR 1.21 (0.30 to 4.98)	21 more per 1000 (from 70 fewer to 398 more)	⊕OOO VERY LOW	CRITICAL
Number of people with 1 or more healthcare consultations (in weeks 5 to 12 from beginning of treatment) - nurse consultations												
1[5]	randomised trials	serious[6]	NA	no serious indirectness	very serious[7]	none	4/26 (15.4%)	3/21 (14.3%)	RR 1.08 (0.27 to 4.29)	11 more per 1000 (from 104 fewer to 470 more)	⊕OOO VERY LOW	CRITICAL
Number of people with 1 or more healthcare consultations (within 4 weeks from beginning of treatment) - any primary care consultations[9]												
1[5]	randomised trials	serious[6]	NA	no serious indirectness	very serious[7]	none	14/33 (42.4%)	12/30 (40.0%)	RR 1.06 (0.59 to 1.92)	24 more per 1000 (from 164 fewer to 368 more)	⊕OOO VERY LOW	CRITICAL
Number of people with 1 or more healthcare consultations (in weeks 5 to 12 from beginning of treatment) - any primary care consultations[9]												
1[5]	randomised trials	serious[6]	NA	no serious indirectness	very serious[7]	none	18/26 (69.2%)	13/21 (61.9%)	RR 1.12 (0.73 to 1.71)	74 more per 1000 (from 167 fewer to 440 more)	⊕OOO VERY LOW	CRITICAL
Number of people with 1 or more healthcare consultations (within 4 weeks from beginning of treatment) - any secondary care consultation[10]												
1[5]	randomised trials	serious[6]	NA	no serious indirectness	very serious[7]	none	1/33 (3.0%)	3/30 (10.0%)	RR 0.30 (0.03 to 2.76)	70 fewer per 1000 (from 97 fewer to 176 more)	⊕OOO VERY LOW	CRITICAL
Number of people with 1 or more healthcare consultations (in weeks 5 to 12 from beginning of treatment) - any secondary care consultation[10]												
1[5]	randomised trials	serious[6]	NA	no serious indirectness	very serious[7]	none	4/26 (15.4%)	2/21 (9.5%)	RR 1.62 (0.33 to 7.98)	59 more per 1000 (from 64 fewer to 665 more)	⊕OOO VERY LOW	CRITICAL
Number of people with 1 or more eczema-related prescriptions (within 3 months from beginning of treatment) - prescription for topical antibiotic and steroid combination												
1[5]	randomised trials	serious[6]	NA	no serious indirectness	very serious[11]	none	8/33 (24.2%)	3/33 (9.1%)	RR 2.67 (0.77 to 9.18)	152 more per 1000 (from 21 fewer to 744 more)	⊕OOO VERY LOW	CRITICAL
Number of people with 1 or more eczema-related prescriptions (within 3 months from beginning of treatment) - prescription for oral antibiotic												
1[5]	randomised trials	serious[6]	NA	no serious indirectness	very serious[7]	none	6/33 (18.2%)	7/33 (21.2%)	RR 0.86 (0.32 to 2.28)	30 fewer per 1000 (from 144 fewer to 272 more)	⊕OOO VERY LOW	CRITICAL
Number of people with 1 or more eczema-related prescriptions (within 3 months from beginning of treatment) - prescription for topical antibiotic												
1[5]	randomised trials	serious[6]	NA	no serious indirectness	very serious[7]	none	1/33 (3.0%)	2/33 (6.1%)	RR 0.50 (0.05 to 5.25)	30 fewer per 1000 (from 58 fewer to 258 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval, NA – not applicable, RR – relative risk

[1] Flucloxacillin suspension, 250 mg/5 ml, 2.5 ml 4 times a day (children aged 3 months to 2 years) or 5 ml 4 times a day (children aged > 2 years to < 8 years)

[2] All participants received topical steroids (clobetasone butyrate 0.05% cream or ointment for use of trunk/limbs and/or hydrocortisone 1% cream or ointment for use on face, applied once a day for 14 days) and were encouraged to use emollients.
[3] Fusidic acid 2% cream applied to affected area(s) 3 times a day for 7 days
[4] Includes face-to-face and over the telephone consultations
[5] Francis et al. 2016
[6] Downgraded 1 level - baseline imbalance in severity (mean POEM score: oral antibiotic group 14.62, topical antibiotic group 16.90) and potential attrition bias (loss to follow-up or withdrawal over 2 weeks/3 months: oral antibiotic group 6%/22%, topical antibiotic group 16%/43%)
[7] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[8] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with oral antibiotics
[9] Includes GP, nurse, pharmacist, NHS direct, walk-in centre and health visitor consultations
[10] Includes outpatient, accident and emergency and inpatient care
[11] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with oral antibiotics; very wide confidence interval

Table 17: GRADE profile – Oral cefalexin compared with topical mupirocin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cefalexin[1]	Topical mupirocin[2]	Relative (95% CI)	Absolute		
Clinical success at the end of treatment - per protocol population												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	31/38 (81.6%)	39/44 (88.6%)	RR 0.92 (0.77 to 1.11)	71 fewer per 1000 (from 204 fewer to 98 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical success at the end of treatment - intention to treat population												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	44/77 (57.1%)	52/82 (63.4%)	RR 0.90 (0.70 to 1.16)	63 fewer per 1000 (from 190 fewer to 101 more)	⊕⊕OO LOW	CRITICAL
Bacteriological eradication or improvement at the end of therapy												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	13/47 (27.7%)	24/48 (50.0%)	RR 2.11 (1.25 to 3.55)	225 fewer per 1000 (from 25 fewer to 340 fewer)	⊕⊕OO LOW	CRITICAL
Number of *Staphylococcus aureus* isolates eradicated or improved at end of therapy in people with *S. aureus* isolated at pre-therapy												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	19/37 (51.4%)	26/37 (70.3%)	RR 0.73 (0.50 to 1.07)	190 fewer per 1000 (from 351 fewer to 49 more)	⊕⊕OO LOW	CRITICAL
Number of *Staphylococcus aureus* isolates persistently eradicated or improved at follow-up (7 to 9 days after end of therapy) in people with *S. aureus* isolated at pre-therapy												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	11/37 (29.7%)	20/37 (54.1%)	RR 1.82 (1.02 to 3.24)	243 fewer per 1000 (from 11 fewer to 373 fewer)	⊕⊕OO LOW	CRITICAL
Number of Acinetobacter lwoffi isolates eradicated or improved at end of therapy in people with A. lwoffi isolated at pre-therapy												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[6]	none	4/7 (57.1%)	1/1 (100%)	RR 0.75 (0.27 to 2.05)	250 fewer per 1000 (from 730 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cefalexin[1]	Topical mupirocin[2]	Relative (95% CI)	Absolute		
Number of Acinetobacter lwoffi isolates persistently eradicated or improved at follow-up (7 to 9 days after end of therapy) in people with A. lwoffi isolated at pre-therapy												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[6]	none	2/7 (28.6%)	0/1 (0%)	RR 1.25 (0.09 to 17.02)	-	⊕OOO VERY LOW	CRITICAL
Number of Enterococcus species isolates eradicated or improved at end of therapy in people with Enterococcus species isolated at pre-therapy												
1[3]	randomised trials	serious[5]	NA	no serious indirectness	very serious[6]	none	2/2 (100%)	1/4 (25%)	RR 2.78 (0.66 to 11.62)	445 more per 1000 (from 85 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Number of Enterococcus species isolates persistently eradicated or improved at follow-up (7 to 9 days after end of therapy) in people with Enterococcus species isolated at pre-therapy												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[6]	none	1/2 (50%)	1/4 (25%)	RR 2.00 (0.22 to 17.89)	250 more per 1000 (from 195 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Number of Moraxella osloensis isolates eradicated or improved at end of therapy in people with M. osloensis isolated at pre-therapy												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[6]	none	2/3 (66.7%)	0/2 (0%)	RR 3.75 (0.27 to 52.64)	-	⊕OOO VERY LOW	CRITICAL
Number of Moraxella osloensis isolates persistently eradicated or improved at follow-up (7 to 9 days after end of therapy) in people with M. osloensis isolated at pre-therapy												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[6]	none	1/3 (33.3%)	0/2 (0%)	RR 2.25 (0.13 to 38.09)	-	⊕OOO VERY LOW	CRITICAL
Number of Flavimonas oryzihabitans isolates eradicated or improved at end of therapy in people with F. oryzihabitans isolated at pre-therapy												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[6]	none	1/3 (33.3%)	1/2 (50%)	RR 0.67 (0.08 to 5.54)	165 fewer per 1000 (from 460 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Number of Flavimonas oryzihabitans isolates persistently eradicated or improved at follow-up (7 to 9 days after end of therapy) in people with F. oryzihabitans isolated at pre-therapy												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[6]	none	0/3 (0%)	1/2 (50%)	RR 0.25 (0.01 to 4.23)	375 fewer per 1000 (from 495 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Number of adverse events												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[6]	none	10/77 (13.0%)	7/82 (8.5%)	RR 1.52 (0.61 to 3.80)	44 more per 1000 (from 33 fewer to 239 more)	⊕OOO VERY LOW	CRITICAL
Number of application site reactions												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[6]	none	0/77 (0%)	2/82 (2.4%)	RR 0.21 (0.01 to 4.36)	19 fewer per 1000 (from 24 fewer to 82 more)	⊕OOO VERY LOW	CRITICAL
Patient preference for treatment[7]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cefalexin[1]	Topical mupirocin[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	very serious[8]	NA	no serious indirectness	serious[9]	none	N= 77	N= 82	95/145 (65.5%) preferred topical 50/145 (34.4%) preferred oral 14/145 (9.7%) did not state a preference		⊕OOO VERY LOW	IMPORTANT

[1] Oral cefalexin, 250 mg 4 times a day and placebo cream 3 times a day for 10 days
[2] Topical mupirocin 2% cream 3 times a day plus oral placebo 4 times a day for 10 days
[3] Rist et al. 2001
[4] Downgraded 1 level - sample size does not reach recruitment aim; study funded by pharmaceutical company; high attrition rate of 48%, although attrition was even across groups
[5] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with topical antibiotics
[6] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[7] At end of therapy, all participants asked: 'Do you prefer oral or topical therapy?'
[8] Downgraded 2 levels - subjective outcome which is likely to be influenced by the treatment received
[9] Downgraded 1 level – not assessable

Appendix H: Excluded studies

Study reference	Reason for exclusion
Bath-Hextall, F.J., Birnie, A.J., Ravenscroft, J.C. et al. (2010) Interventions to reduce Staphylococcus aureus in the management of atopic eczema: An updated Cochrane review. British Journal of Dermatology 163(1): 12-26	- Duplicate reference [Also included in SR database]
Bath-Hextall, F.J., Birnie, A.J., Ravenscroft, J.C. et al. (2010) Interventions to reduce Staphylococcus aureus in the management of atopic eczema: An updated Cochrane review. British Journal of Dermatology 163(1): 12-26	- More recent systematic review included that covers the same topic
Birnie, Andrew J, Bath-Hextall, Fiona J, Ravenscroft, Jane Catherine et al. (2008) Interventions to reduce Staphylococcus aureus in the management of atopic eczema. The Cochrane database of systematic reviews: cd003871	- Duplicate reference [Also included in SR database]
Birnie, Andrew J, Bath-Hextall, Fiona J, Ravenscroft, Jane Catherine et al. (2008) Interventions to reduce Staphylococcus aureus in the management of atopic eczema. The Cochrane database of systematic reviews: cd003871	- More recent systematic review included that covers the same topic
Bonamonte, D, Belloni Fortina, A, Neri, L et al. (2014) Fusidic acid in skin infections and infected atopic eczema. Giornale italiano di dermatologia e venereologia: organo ufficiale, Societa italiana di dermatologia e sifilografia 149(4): 453-9	- Review article but not a systematic review [No description of methods and narrative summary]
Bonamonte, D, Belloni Fortina, A, Neri, L et al. (2014) Fusidic acid in skin infections and infected atopic eczema. Giornale italiano di dermatologia e venereologia: organo ufficiale, Societa italiana di dermatologia e sifilografia 149(4): 453-9	- Duplicate reference [Also included in RCT database]
Claudy, A (2001) Comparative study of fusidic acid versus pristinamycin in skin infections requiring an oral antibiotherapy. Presse medicale 30(8): 364-368	- Study not reported in English
Claudy, A (2001) Superficial pyoderma requiring oral antibiotic therapy: fusidic acid versus pristinamycin]. Presse medicale (Paris, France: 1983) 30(8): 364-368	- Duplicate reference [Duplicate of Claudy et al. 2001 "Comparative study of fusidic acid versus pristinamycin in skin infections requiring an oral antibiotherapy"]
Corey, G Ralph, Good, Samantha, Jiang, Hai et al. (2015) Single-dose oritavancin versus 7-10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 60(2): 254-62	- Does not contain a population of people with secondary infection of a skin condition [Includes people with SSTI infection, no mention of secondary infection]
Covington, Paul, Davenport, J Michael, Andrae, David et al. (2011) Randomized, double-blind, phase II, multicenter study evaluating the safety/tolerability and efficacy of JNJ-Q2, a novel fluoroquinolone, compared with linezolid for treatment of acute bacterial skin and skin structure infection. Antimicrobial agents and chemotherapy 55(12): 5790-7	- Does not contain a population of people with secondary infection of a skin condition [Includes people with wound infections, cellulites and severe abscess - no mention of secondary infection of these conditions]
Dodds, Tristan John and Hawke, Catherine Isobel (2009) Linezolid versus vancomycin for MRSA skin and soft tissue infections (systematic review and meta-analysis). ANZ journal of surgery 79(9): 629-35	- Does not contain a population of people with secondary infection of a skin condition

Study reference	Reason for exclusion
Dunn C, J (2006) Tigecycline: an evidence-based review of its antibacterial activity and effectiveness in complicated skin and soft tissue and intraabdominal infections. Core Evidence 1(3): 181-194	- Review article but not a systematic review - Does not contain a population of people with secondary infection of a skin condition
Dupire, Gwendy, Droitcourt, Catherine, Hughes, Carolyn et al. (2019) Antistreptococcal interventions for guttate and chronic plaque psoriasis. The Cochrane database of systematic reviews 3: cd011571	- Does not contain a population of people with secondary infection of a skin condition
Eichenfield, L.F., Bieber, T., Beck, L.A. et al. (2019) Infections in Dupilumab Clinical Trials in Atopic Dermatitis: A Comprehensive Pooled Analysis. American Journal of Clinical Dermatology 20(3): 443-456	- Study does not contain a relevant intervention [Looks at dupilumab (antibody) for the prevention of infection of eczema, not treatment of infected eczema]
Eichenfield, L.F., Bieber, T., Beck, L.A. et al. (2019) Infections in Dupilumab Clinical Trials in Atopic Dermatitis: A Comprehensive Pooled Analysis. American Journal of Clinical Dermatology 20(3): 443-456	- Duplicate reference [Also included in RCT database]
Fahimi, Jahan; Singh, Amandeep; Frazee, Bradley W (2015) The role of adjunctive antibiotics in the treatment of skin and soft tissue abscesses: a systematic review and meta-analysis. CJEM 17(4): 420-32	- Does not contain a population of people with secondary infection of a skin condition
Francis, Nick A, Ridd, Matthew J, Thomas-Jones, Emma et al. (2016) A randomised placebo-controlled trial of oral and topical antibiotics for children with clinically infected eczema in the community: the ChildRen with Eczema, Antibiotic Management (CREAM) study. Health technology assessment (Winchester, England) 20(19): i-84	- Duplicate reference [Also included in SR database]
Francis, Nick A, Ridd, Matthew J, Thomas-Jones, Emma et al. (2016) A randomised placebo-controlled trial of oral and topical antibiotics for children with clinically infected eczema in the community: the ChildRen with Eczema, Antibiotic Management (CREAM) study. Health technology assessment (Winchester, England) 20(19): i-84	- Duplicate reference [Duplicate of Francis et al 2016 included in RCT database]
Francis, Nick A, Ridd, Matthew J, Thomas-Jones, Emma et al. (2017) Oral and Topical Antibiotics for Clinically Infected Eczema in Children: A Pragmatic Randomized Controlled Trial in Ambulatory Care. Annals of family medicine 15(2): 124-130	- Duplicate reference
Fritz, Stephanie A, Hogan, Patrick G, Camins, Bernard C et al. (2013) Mupirocin and chlorhexidine resistance in Staphylococcus aureus in patients with community-onset skin and soft tissue infections. Antimicrobial agents and chemotherapy 57(1): 559-68	- Does not contain a population of people with secondary infection of a skin condition [SSTI but no mention of secondary infection]
Fuentes Sermeno, L; Briseno Rodriguez, G; Hernandez Arana, S (2001) An open, comparative, randomized study about oral ambulatory therapy with levofloxacine vs ciprofloxacine in complicated infections of skin and soft tissues. Investigacion medica internacional 28(1): 21-27	- Study not reported in English
Girolomoni, G, Mattina, R, Manfredini, S et al. (2016) Fusidic acid betamethasone lipid cream. International journal of clinical practice 70suppl184: 4-13	- Review article but not a systematic review
Gong, J Q, Lin, L, Lin, T et al. (2006) Skin colonization by Staphylococcus aureus in patients with eczema and atopic dermatitis and relevant combined topical therapy: a double-blind multicentre randomized controlled trial. The British journal of dermatology 155(4): 680-7	- Does not contain a population of people with secondary infection of a skin condition [Eczema, no mention of secondary infection, and

Study reference	Reason for exclusion
	discussion section indicates that it doesn't include secondary infection]
Gong, J Q, Lin, L, Lin, T et al. (2006) Skin colonization by Staphylococcus aureus in patients with eczema and atopic dermatitis and relevant combined topical therapy: a double-blind multicentre randomized controlled trial. The British journal of dermatology 155(4): 680-7	- Duplicate reference [Also included in RCT database]
Hoare, C.; Li Wan Po, A.; Williams, H. (2000) Systematic review of treatments for atopic eczema. Health Technology Assessment 4(37)	- More recent systematic review included that covers the same topic
Huang, Jennifer T, Abrams, Melissa, Tlougan, Brook et al. (2009) Treatment of Staphylococcus aureus colonization in atopic dermatitis decreases disease severity. Pediatrics 123(5): e808-14	- RCT included in an included systematic review
Huang, Jennifer T, Abrams, Melissa, Tlougan, Brook et al. (2009) Treatment of Staphylococcus aureus colonization in atopic dermatitis decreases disease severity. Pediatrics 123(5): e808-14	- Duplicate reference [Also included in RCT database]
Hung, Shuo-Hsun, Lin, Yu-Tsan, Chu, Chia-Yu et al. (2007) Staphylococcus colonization in atopic dermatitis treated with fluticasone or tacrolimus with or without antibiotics. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology 98(1): 51-6	- Does not contain a population of people with secondary infection of a skin condition [Study excludes people with an obvious infection which requires antibiotics]
Janis, Jeffrey E, Hatef, Daniel A, Reece, Edward M et al. (2014) Does empiric antibiotic therapy change MRSA [corrected] hand infection outcomes? Cost analysis of a randomized prospective trial in a county hospital. Plastic and reconstructive surgery 133(4): 511e-8e	- Does not contain a population of people with secondary infection of a skin condition [Population doesn't include secondary infection; population is hand infections, including abscess, infected wound and bite]
Khobragade, Kunal J (2005) Efficacy and safety of combination ointment "fluticasone propionate 0.005% plus mupirocin 2.0%" for the treatment of atopic dermatitis with clinical suspicion of secondary bacterial infection: an open label uncontrolled study. Indian journal of dermatology, venereology and leprology 71(2): 91-5	- Not a relevant study design [Non-randomised trial]
Khobragade, Kunal J (2005) Efficacy and safety of combination ointment "fluticasone propionate 0.005% plus mupirocin 2.0%" for the treatment of atopic dermatitis with clinical suspicion of secondary bacterial infection: an open label uncontrolled study. Indian journal of dermatology, venereology and leprology 71(2): 91-5	- Duplicate reference [Also included in RCT database]
Lubbe, J (2003) Secondary infections in patients with atopic dermatitis. American journal of clinical dermatology 4(9): 641-654	- Review article but not a systematic review
Narayanan, V., Motlekar, S., Kadhe, G. et al. (2014) Efficacy and Safety of Nadifloxacin for Bacterial Skin Infections: Results from Clinical and Post-Marketing Studies. Dermatology and Therapy 4(2)	- Not a relevant study design [Pooled analysis of 3 RCTs and an observational study which cannot be disaggregated in results] - Does not contain a population of people with secondary infection of a skin condition [Cannot disaggregate results for relevant and non-relevant

Study reference	Reason for exclusion
	skin infections; 6.25% of population has infected scabies and 5.9% infected dermatoses (data from observational study)]
Noel, Gary J, Draper, Michael P, Hait, Howard et al. (2012) A randomized, evaluator-blind, phase 2 study comparing the safety and efficacy of omadacycline to those of linezolid for treatment of complicated skin and skin structure infections. Antimicrobial agents and chemotherapy 56(11): 5650-4	- Does not contain a population of people with secondary infection of a skin condition [People with SSSI -wound infection, major abscess, infected leg ulcer or cellulitis - not secondary infection]
Owen, C M, Chalmers, R J, O'Sullivan, T et al. (2001) A systematic review of antistreptococcal interventions for guttate and chronic plaque psoriasis. The British journal of dermatology 145(6): 886-90	- Does not contain a population of people with secondary infection of a skin condition [Psoriasis (and aiming to reduce staphylococcal colonization) but no mention of infection]
Parish, Lawrence Charles, Jorizzo, Joseph Lucius, Breton, John Jeffrey et al. (2006) Topical retapamulin ointment (1%, wt/wt) twice daily for 5 days versus oral cephalexin twice daily for 10 days in the treatment of secondarily infected dermatitis: results of a randomized controlled trial. Journal of the American Academy of Dermatology 55(6): 1003-13	- Study does not contain a relevant intervention [Retapamulin is not available in UK]
Parish, Lawrence Charles, Jorizzo, Joseph Lucius, Breton, John Jeffrey et al. (2006) Topical retapamulin ointment (1%, wt/wt) twice daily for 5 days versus oral cephalexin twice daily for 10 days in the treatment of secondarily infected dermatitis: results of a randomized controlled trial. Journal of the American Academy of Dermatology 55(6): 1003-13	- Duplicate reference
Ravenscroft, J C, Layton, A M, Eady, E A et al. (2003) Short-term effects of topical fusidic acid or mupirocin on the prevalence of fusidic acid resistant (FusR) Staphylococcus aureus in atopic eczema. The British journal of dermatology 148(5): 1010-7	- Does not contain a population of people with secondary infection of a skin condition
Shorr A F, Kunkel M J, Kollef M (2005) Linezolid versus vancomycin for Staphylococcus aureus bacteraemia: pooled analysis of randomized studies. Journal of Antimicrobial Chemotherapy 56(5): 923-929	- Does not contain a population of people with secondary infection of a skin condition [Includes secondary blood infection from pneumonia, UTI and skin and soft tissue infections - no mention of secondary infection from a common skin infection]
Talan, David A, Lovecchio, Frank, Abrahamian, Fredrick M et al. (2016) A Randomized Trial of Clindamycin Versus Trimethoprim-sulfamethoxazole for Uncomplicated Wound Infection. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 62(12): 1505-1513	- Does not contain a population of people with secondary infection of a skin condition [Study population is infected wounds. Does include 11/401 participants who also have eczema or other chronic skin infection, but no mention that for this population the wound in question is from a skin condition. No results reported separately for this population]

Study reference	Reason for exclusion
Tanus, Tonny, Scangarella-Oman, Nicole E, Dalessandro, Marybeth et al. (2014) A randomized, double-blind, comparative study to assess the safety and efficacy of topical retapamulin ointment 1% versus oral linezolid in the treatment of secondarily infected traumatic lesions and impetigo due to methicillin-resistant Staphylococcus aureus. Advances in skin & wound care 27(12): 548-59	- Does not contain a population of people with secondary infection of a skin condition [Population is secondary infection of wounds and impetigo, both not relevant conditions]
Thomas, Jackson, Davey, Rachel, Peterson, Gregory M et al. (2018) Treatment of scabies using a tea tree oil-based gel formulation in Australian Aboriginal children: protocol for a randomised controlled trial. BMJ open 8(5): e018507	- Not a relevant study design
Tsai, Ya-Chu and Tsai, Tsen-Fang (2019) A review of antibiotics and psoriasis: induction, exacerbation, and amelioration. Expert review of clinical pharmacology	- Does not contain a population of people with secondary infection of a skin condition [Population includes psoriasis but does not clearly state if this includes infected psoriasis]
Tsoulas, Christos and Nathwani, Dilip (2015) Review of meta-analyses of vancomycin compared with new treatments for Gram-positive skin and soft-tissue infections: Are we any clearer?. International journal of antimicrobial agents 46(1): 1-7	- Does not contain a population of people with secondary infection of a skin condition
Van, T.C., Tat, T.N., Lan, A.T. et al. (2019) Superantigens of staphylococcus aureus colonization in atopic dermatitis and treatment efficacy of oral cefuroxime in Vietnamese patients. Open Access Macedonian Journal of Medical Sciences 7(2): 243-246	- Does not contain a population of people with secondary infection of a skin condition [Specifically excludes people with infected eczema]
Wasilewski, M, Wilson, M G, Sides, G D et al. (2000) Comparative efficacy of 5 days of dirithromycin and 7 days of erythromycin in skin and soft tissue infections. The Journal of antimicrobial chemotherapy 46(2): 255-62	- Does not contain a population of people with secondary infection of a skin condition [Includes people with secondary skin and soft tissue infections, not secondary infection of these conditions]
Wernham, A.G.H., Veitch, D., Grindlay, D.J.C. et al. (2019) What's new in atopic eczema? An analysis of systematic reviews published in 2017. Part 1: treatment and prevention. Clinical and Experimental Dermatology	- Review article but not a systematic review [No description of methods e.g. no description of systematic searches for included data; no quantitative data analysis with limited narrative analysis]
Wible, Kenneth, Tregnaghi, Miguel, Bruss, Jon et al. (2003) Linezolid versus cefadroxil in the treatment of skin and skin structure infections in children. The Pediatric infectious disease journal 22(4): 315-23	- Does not contain a population of people with secondary infection of a skin condition [Excludes people with chronic inflammatory skin conditions (e.g. super infected eczema)]
Wilcox, M.; Nathwani, D.; Dryden, M. (2004) Linezolid compared with teicoplanin for the treatment of suspected for proven Gram-positive infections. Journal of Antimicrobial Chemotherapy 53(2): 335-344	- Does not contain a population of people with secondary infection of a skin condition [Includes severe infections, such as hospital acquired pneumonia, and severe SSTI - but no mention of secondary infection of a skin condition]