National Institute for Health and Care Excellence

NICE guideline NG153

Impetigo: antimicrobial prescribing guideline

Evidence review

February 2020

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The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN: 978-1-4731-3680-9

Contents

1 Context

1.1 Background

Impetigo is a common bacterial infection of the skin (Clinical Knowledge Summary [CKS] – impetigo, 2018). It is contagious, with transmission occurring through direct contact with an infected person or indirectly through contaminated objects such as toys, clothing or towels. Bacteria usually enter the skin through breaks caused by minor trauma such as insect bites or scratches or underlying skin conditions such as eczema or scabies (secondary impetigo; CKS – impetigo, 2018), but can also invade normal skin (primary impetigo; British Skin Foundation – Impetigo). It affects all age groups, however it is most common in young children, with weekly rates in England and Wales highest in children aged 0 to 4 years (84 per 100,000) and children aged 5 to 14 years (3.6 per 100,000; Elliot et al. 2006). Impetigo is the most common bacterial skin infection in children aged 2 to 5 years (Hartman-Adams et al. 2014).

Presentation of impetigo is mainly characterised by thin-walled vesicles or larger bullae and blisters forming, which rupture to leave a superficial erosion covered with yellowish-brown crusts. Lesions can be painful and itchy and usually form on the face and on hands (Koning et al. 2012). In more severe cases of impetigo, bullae can persist for several days and rupture leaving raw skin which eventually forms crusts. Systemic symptoms (weakness, fever and diarrhoea) are more common if large areas of skin are affected (CKS – impetigo, 2018).

Diagnosis of impetigo is usually made through clinical examination and differential diagnosis based on presentation and history. Further investigations are not usually needed to confirm diagnosis (CKS – impetigo, 2018).

Bullous impetigo (a less prevalent and more severe form of impetigo) is caused by *Staphylococcus aureus*, whereas non-bullous impetigo is caused by *Staphylococcus aureus*, *Streptococcus pyogenes* or a combination of both pathogens.

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 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 9.0% from 2014 to 2018. This reflected a 16.7% decrease in primary care and a 2.8% increase in secondary care prescribing. In 2018, the most commonly used antibiotics were: penicillins (38.4%), tetracyclines (25.2%) and macrolides (15.8%).

Over the 5-year period from 2014 to 2018, significant declining trends of use were seen for penicillins, first and second-generation cephalosporins, tetracyclines, macrolides, sulfonamides and trimethoprim, and oral metronidazole. In contrast, use of third, fourth and fifth-generation cephalosporins and other antibacterials (including nitrofurantoin) significantly increased.

In the 5-year period from 2014 to 2018, use of penicillins declined by 14.2% in the GP setting and by 18.4% in the dental setting, but increased by 32.3% in other community settings and by 7.9% in hospital inpatients. Prescribing of co-amoxiclav and amoxicillin between 2014 and 2018 decreased by 9.9% and 16.7%, respectively. The use of pivmecillinam increased steadily, most likely for use in urinary tract infection; and piperacillin with tazobactam use decreased by 31.7% over the 5-year period, with a sharp reduction in 2017 due to the shortage of international supply and a subsequent 6.4% increase from 2017 to 2018.

Overall use of tetracyclines reduced slightly (by 6.8%) between 2014 and 2018, but doxycycline use in particular increased. Macrolide use declined by 14.6% from 2014 to 2018, largely because of a decrease in erythromycin use. Azithromycin use, however, continued to increase.

For the 7 priority bacterial pathogens reported, the rate of bloodstream infection in 2018 was 145 per 100,000 of the population (a 22% increase from 2014). However, *Escherichia coli* was the most common cause of blood stream infection (76.0 cases per 100,000 population). For the most common causative organism of impetigo – *Staphylococcus aureus* – ESPAUR 2019 reports that there was little change in the proportion of blood stream infections that were methicillin-resistant between 2014 (7.5%) and 2018 (6.7%). Resistance to daptomycin and linezolid remained low in *Staphylococcus aureus* bacteraemia in 2018, with less than 1% resistance reported for both antibiotics.

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 impetigo (see appendix C: literature search strategy for full details). The literature search identified 2,416 references. These references were screened using their titles and abstracts and 114 full text references were obtained and assessed for relevance. Nine 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. Four of the 9 references were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix F: included studies).

The 5 references that were not prioritised for inclusion are listed in appendix I: studies not prioritised, with reasons for not prioritising the studies. Also see appendix E: evidence prioritisation for more information on study selection.

The remaining 105 references were excluded. These are listed in appendix J: 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 F: included studies. An overview of the quality assessment of each included study is shown in appendix G: quality assessment of included studies.

Table 1: Summary of included studies

Study	Number of participants	Population	Intervention	Comparison	Key outcomes
Al-Samman et al. 2014 RCT	N=52	Children aged 2 to 9 years with moderate impetigo	Intramuscular ceftriaxone	Oral cefadroxil	Treatment success (day 8)
Bowen et al. 2014 Non-inferiority RCT	N=508	Children aged 4 to10 years with mild to moderate impetigo	Intramuscular benzylpenicillin	Oral co-trimoxazole	Treatment success (day 7), adverse events
Hebert et al. 2018 Post-hoc analysis of 2 RCTs	N=877	Adults, young people and children with impetigo (severity not defined)	Topical ozenoxacin[1]	Placebo	Clinical success (day 7)
Koning et al. 2012 Systematic review	68 RCTs N=5,578	Adults, young people and children with impetigo (severity not defined)	Topical antibiotics (mupirocin, fusidic acid, gentamicin, chloramphenicol), oral antibiotics (penicillins, macrolides, cephalosporins), oral and topical antibiotic combinations (cefdinir, minomycin or fosfomycin plus tetracycline) and intramuscular antibiotics (cephalosporins and penicillins)	Topical antibiotics (betamethasone valerate, fusidic acid, neomycin, polymyxin B/neomycin, neomycin/bacitracin, neomycin), antiseptics, antifungals, oral antibiotics (penicillins, macrolides, cephalosporins, co-trimoxazole) or placebo	Cure or improvement (day 7), adverse events
Abbreviations: RCT – randomised control trial					
[1] Topical ozenoxacin is licensed but at publication is not available in the UK					

3 Evidence summary

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

The main results are summarised below for adults, young people and children with impetigo.

See the summaries of product characteristics, British National Formulary (BNF) and BNF for children (BNF-C) 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.

Study details

A systematic review (Koning et al. 2012) makes up a large proportion of the evidence included for the management of impetigo. Koning et al. 2012 included adults, young people and children with non-bullous, bullous and secondary impetigo diagnosed by a medically trained professional. The most common reported cause of impetigo was infection with *Staphylococcus aureus*, followed by *Streptococcus pyogenes* infection.

Approximately half of the studies included in the systematic review were reported as sub-group analysis of participants with impetigo, from studies investigating an intervention for a range of skin infections. Therefore, many of the included studies have small sample sizes leading to being underpowered.

The average age of participants in trials that studied a range of skin infections was usually higher than in studies focusing on impetigo alone. Of the studies investigating impetigo only, no studies were conducted only in adults, 27 studies exclusively included children and young people under 18 years or had an average age of < 10 years and 6 studies included both adults and children and young people (but all of these studies had an average age of < 17 years); 2 studies did not report the age of participants. Where age was not reported for the sub-group analysis of people with impetigo, the age of the population included in the full primary study has been reported. The systematic review does not report analysis based on age.

Cure was the main outcome of interest; however, this was often not defined and primary studies often combined data for 'cured' and 'improved'. The length of follow up ranged from 4 to 24 days, with data for follow up as close as possible to 7 days after the start of the intervention reported.

3.1 Efficacy of antibiotics

3.1.1 Topical antibiotics

The evidence for topical antibiotics compared with placebo for impetigo comes from 1 systematic review and meta-analysis (Koning et al. 2012) and 1 pooled-analysis of 2 RCTs (Hebert et al. 2018).

For details of Koning et al. 2012, see the section on study details.

The pooled-analysis (Hebert et al. 2018) describes the results of 2 RCTs (Rosen et al. 2018 and Gropper et al. 2014), which included adults, young people and children (the majority of participants < 18 years old) with a clinical diagnosis of impetigo. The primary outcome was defined as clinical success at the end of therapy visit (day 7)

based on skin infection rating scale scores (0 for exudates or pus, crusting and itching or pain and ≤ 1 for erythema or inflammation) as well as no need for additional antimicrobial therapy.

Topical antibiotics compared with placebo – overall analysis

A systematic review (Koning et al. 2012) found for an overall analysis of topical antibiotics compared with placebo, that topical antibiotics were more effective than placebo in adults, young people and children with impetigo for cure or improvement at 5 to 12 days follow-up (6 RCTs, n=575, 70.7% versus 29.3%, relative risk [RR] 2.24, 95% confidence interval [CI] 1.61 to 3.13, number needed to treat [NNT] 3, 95% CI 2 to 3; very low quality evidence).

Topical antibiotics included in the analysis were: mupirocin (2% three times a day for 7 to 9 days; 2% once a day until cleared or 2% three times a day for 10 to 12 days); fusidic acid (2% three times a day); topical retapamulin (1% twice a day for 5 days) and bacitracin ointment (application twice a day, unreported concentration or course length).

No safety or tolerability data was reported for the overall analysis.

See GRADE profiles: Table 4Table 4: GRADE profile – topical antibiotics compared with placebo

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Placebo	Relative (95% CI)	Absolute		
Topical antibiotics[1] - cure or improvement – overall analysis												
6[2]	randomised trials	serious[3]	serious[4]	serious[5,6]	no serious imprecision	none	220/312 (70.5%)	77/263 (29.3%)	RR 2.24 (1.61 to 3.13)	363 more per 1000 (from 179 more to 624 more)	⊕OOO VERY LOW	CRITICAL
Fusidic acid[7] - cure or improvement												
1[2]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	42/76 (55.3%)	10/80 (12.5%)	RR 4.42 (2.39 to 8.17)	428 more per 1000 (from 174 more to 896 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mupirocin[8] - cure or improvement												
3[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness[5]	no serious imprecision	none	58/81 (71.6%)	30/92 (32.6%)	RR 2.18 (1.58 to 3.00)	385 more per 1000 (from 189 more to 652 more)	⊕⊕⊕O MODERATE	CRITICAL
Mupirocin[7] - nausea or vomiting												
1[2]	randomised trials	serious[9]	no serious inconsistency	no serious	very serious[10]	none	0/52 (0%)	1/52 (1.9%)	RR 3.00 (0.13	38 more per		CRITICAL

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Placebo	Relative (95% CI)	Absolute		
				indirectness					to 71.99) Peto OR 0.14 (0.00 to 6.82)	1000 (from 17 fewer to 1000 more)	⊕OOO VERY LOW	
Ozenoxacin[11] - clinical success (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	169/357 (47.3%)	111/354 (31.4%)	RR 1.51 (1.25 to 1.82)	160 more per 1000 (from 78 more to 257 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Ozenoxacin[11] - clinical failure (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[13]	none	188/357 (52.7%)	243/354 (68.6%)	RR 0.77 (0.68 to 0.87)	158 fewer per 1000 (from 89 fewer to 220 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Ozenoxacin[11] - microbiological success (day 3 to 4)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	218/279 (78.1%)	134/271 (49.4%)	RR 1.58 (1.38 to 1.81)	287 more per 1000 (from 188 more to 401 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Ozenoxacin[11] - microbiological failure (day 3 to 4)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	53/271 (19.6%)	122/256 (47.7%)	RR 0.41 (0.31 to 0.54)	281 fewer per 1000 (from 219 fewer to 329 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Ozenoxacin[11] - microbiological success (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[14]	none	237/261 (90.8%)	173/248 (69.8%)	RR 1.30 (1.19 to 1.43)	209 more per 1000 (from 133 more to 300 more)	⊕⊕⊕O MODERATE	CRITICAL
Ozenoxacin[11] - microbiological failure (day 6 to 7)												
1[12]	randomised trials	no serious	NA	no serious indirectness	no serious imprecision	none	24/261 (9.2%)	75/248 (30.2%)	RR 0.30 (0.20	212 fewer per 1000	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Placebo	Relative (95% CI)	Absolute		
		risk of bias							to 0.47)	(from 160 fewer to 242 fewer)		
Abbreviations: CI – confidence interval; RR – relative risk; NA – not applicable; OR – odds ratio												

[1] Topical antibiotics include: mupirocin - 2% 3 times a day for 7 to 9 days; 2% once daily until cleared or 2% 3 times daily for 10 to 12 days; fusidic acid - 2% 3 times a day; topical retapamulin - 1% 2 times daily for 5 days; bacitracin ointment, 2 times daily (unreported dose or course length)
[2] Koning et al. 2012
[3] Downgraded 1 level - 1 or more studies included were deemed at high risk of bias in 1 or more domains by systematic review authors
[4] Downgraded 1 level - heterogeneity >50%
[5] Not downgraded - 1 study includes a range of skin infections, with a subgroup for impetigo described separately and reported here
[6] Downgraded 1 level - not all topical antibiotics are available in UK
[7] Fusidic acid - 2% 3 times a day
[8] Mupirocin - 2% 3 times a day for 7 to 9 days; 2% once daily until cleared or 2% 3 times daily for 10 to 12 days
[9] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[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] Ozenoxacin 1% cream - participants instructed to apply thin layer (a fingertip unit, approximately 0.5 g) to the affected areas twice daily
[12] Hebert et al. 2018; pooled-analysis of 2 randomised controlled trials (Rosen et al. 2018 and Gropper et al. 2014)
[13] 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
[14] 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 ozenoxacin

Topical fusidic acid compared with placebo

A systematic review (Koning et al. 2012) found that topical fusidic acid (2% three times a day, unreported course length) was more effective than with placebo in children with impetigo for cure or improvement at 7 days follow-up (1 RCT, n=156, 55.3% versus 12.5%, RR 4.42, 95% CI 2.39 to 8.17, NNT 3, 95% CI 2 to 4; high quality evidence).

No safety or tolerability data was reported.

See GRADE profiles: Table 4Table 4: GRADE profile – topical antibiotics compared with placebo

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Placebo	Relative (95% CI)	Absolute		
Topical antibiotics[1] - cure or improvement – overall analysis												
6[2]	randomised trials	serious[3]	serious[4]	serious[5,6]	no serious imprecision	none	220/312 (70.5%)	77/263 (29.3%)	RR 2.24 (1.61 to 3.13)	363 more per 1000 (from 179 more	⊕OOO VERY LOW	CRITICAL

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1[2]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	42/76 (55.3%)	10/80 (12.5%)	RR 4.42 (2.39 to 8.17)	428 more per 1000 (from 174 more to 896 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mupirocin[8] - cure or improvement												
3[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness[5]	no serious imprecision	none	58/81 (71.6%)	30/92 (32.6%)	RR 2.18 (1.58 to 3.00)	385 more per 1000 (from 189 more to 652 more)	⊕⊕⊕O MODERATE	CRITICAL
Mupirocin[7] - nausea or vomiting												
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Ozenoxacin[11] - clinical success (day 6 to 7)												
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Ozenoxacin[11] - clinical failure (day 6 to 7)												
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Abbreviations: CI – confidence interval; RR – relative risk; NA – not applicable; OR – odds ratio												

[1] Topical antibiotics include: mupirocin - 2% 3 times a day for 7 to 9 days; 2% once daily until cleared or 2% 3 times daily for 10 to 12 days; fusidic acid - 2% 3 times a day; topical retapamulin - 1% 2 times daily for 5 days; bacitracin ointment, 2 times daily (unreported dose or course length)
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Topical mupirocin compared with placebo

A systematic review (Koning et al. 2012) found that topical mupirocin (2% three times a day for 7 to 9 days; 2% once daily until cleared or 2% three times a day for 10 to 12

days) was more effective than placebo in adults, young people and children with impetigo for cure or improvement at 7 to 12 days follow-up (3 RCTs, n=173, 71.6% versus 32.6%, RR 2.18, 95% CI 1.58 to 3.00, NNT 3, 95% CI 2 to 4; moderate quality evidence).

There was no significant difference in the number of people reporting nausea or vomiting between topical mupirocin and placebo (1 RCT, n=104, 0% versus 1.9%, RR 3.00, 95% CI 0.13 to 71.99; very low quality evidence).

See GRADE profiles: Table 4Table 4: GRADE profile – topical antibiotics compared with placebo

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1[2]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	42/76 (55.3%)	10/80 (12.5%)	RR 4.42 (2.39 to 8.17)	428 more per 1000 (from 174 more to 896 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mupirocin[8] - cure or improvement												
3[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness[5]	no serious imprecision	none	58/81 (71.6%)	30/92 (32.6%)	RR 2.18 (1.58 to 3.00)	385 more per 1000 (from 189 more to 652 more)	⊕⊕⊕O MODERATE	CRITICAL
Mupirocin[7] - nausea or vomiting												
1[2]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[10]	none	0/52 (0%)	1/52 (1.9%)	RR 3.00 (0.13 to 71.99) Peto OR 0.14 (0.00 to 6.82)	38 more per 1000 (from 17 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Ozenoxacin[11] - clinical success (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	169/357 (47.3%)	111/354 (31.4%)	RR 1.51 (1.25 to 1.82)	160 more per 1000 (from 78	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Placebo	Relative (95% CI)	Absolute		
										more to 257 more)		
Ozenoxacin[11] - clinical failure (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[13]	none	188/357 (52.7%)	243/354 (68.6%)	RR 0.77 (0.68 to 0.87)	158 fewer per 1000 (from 89 fewer to 220 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Ozenoxacin[11] - microbiological success (day 3 to 4)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	218/279 (78.1%)	134/271 (49.4%)	RR 1.58 (1.38 to 1.81)	287 more per 1000 (from 188 more to 401 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Ozenoxacin[11] - microbiological failure (day 3 to 4)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	53/271 (19.6%)	122/256 (47.7%)	RR 0.41 (0.31 to 0.54)	281 fewer per 1000 (from 219 fewer to 329 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Ozenoxacin[11] - microbiological success (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[14]	none	237/261 (90.8%)	173/248 (69.8%)	RR 1.30 (1.19 to 1.43)	209 more per 1000 (from 133 more to 300 more)	⊕⊕⊕O MODERATE	CRITICAL
Ozenoxacin[11] - microbiological failure (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	24/261 (9.2%)	75/248 (30.2%)	RR 0.30 (0.20 to 0.47)	212 fewer per 1000 (from 160 fewer to 242 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Abbreviations: CI – confidence interval; RR – relative risk; NA – not applicable; OR – odds ratio

[1] Topical antibiotics include: mupirocin - 2% 3 times a day for 7 to 9 days; 2% once daily until cleared or 2% 3 times daily for 10 to 12 days; fusidic acid - 2% 3 times a day; topical retapamulin - 1% 2 times daily for 5 days; bacitracin ointment, 2 times daily (unreported dose or course length)

[2] Koning et al. 2012

[3] Downgraded 1 level - 1 or more studies included were deemed at high risk of bias in 1 or more domains by systematic review authors

[4] Downgraded 1 level - heterogeneity >50%

[5] Not downgraded - 1 study includes a range of skin infections, with a subgroup for impetigo described separately and reported here

[6] Downgraded 1 level - not all topical antibiotics are available in UK

[7] Fusidic acid - 2% 3 times a day
[8] Mupirocin - 2% 3 times a day for 7 to 9 days; 2% once daily until cleared or 2% 3 times daily for 10 to 12 days
[9] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[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] Ozenoxacin 1% cream - participants instructed to apply thin layer (a fingertip unit, approximately 0.5 g) to the affected areas twice daily
[12] Hebert et al. 2018; pooled-analysis of 2 randomised controlled trials (Rosen et al. 2018 and Gropper et al. 2014)
[13] 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
[14] 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 ozenoxacin

Topical ozenoxacin compared with placebo

A pooled-analysis of 2 RCTs (Hebert et al. 2018) found that topical ozenoxacin was more effective than placebo in children with impetigo for clinical success at 7 days follow-up (1 RCT, n=711, 47.3% versus 31.4%, RR 1.51, 95% CI 1.25 to 1.82, NNT 7, 95% CI 5 to 12; high quality evidence) and microbiological success at day 6 or 7 (1 RCT, n=509, 90.8% versus 69.8%, RR 1.30, 95% CI 1.19 to 1.43, NNT 5, 95% CI 4 to 7; moderate quality evidence). Topical ozenoxacin used was 1% cream, applied in a thin layer (a fingertip unit, approximately 0.5 g) to the affected areas twice a day.

No safety or tolerability data was reported.

See GRADE profiles: Table 4Table 4: GRADE profile – topical antibiotics compared with placebo

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Placebo	Relative (95% CI)	Absolute		
Topical antibiotics[1] - cure or improvement – overall analysis												
6[2]	randomised trials	serious[3]	serious[4]	serious[5,6]	no serious imprecision	none	220/312 (70.5%)	77/263 (29.3%)	RR 2.24 (1.61 to 3.13)	363 more per 1000 (from 179 more to 624 more)	⊕OOO VERY LOW	CRITICAL
Fusidic acid[7] - cure or improvement												
1[2]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	42/76 (55.3%)	10/80 (12.5%)	RR 4.42 (2.39 to 8.17)	428 more per 1000 (from 174 more to 896 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mupirocin[8] - cure or improvement												
3[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness[5]	no serious imprecision	none	58/81 (71.6%)	30/92 (32.6%)	RR 2.18 (1.58 to 3.00)	385 more per 1000 (from 189 more to 652 more)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Placebo	Relative (95% CI)	Absolute		
Mupirocin[7] - nausea or vomiting												
1[2]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[10]	none	0/52 (0%)	1/52 (1.9%)	RR 3.00 (0.13 to 71.99) Peto OR 0.14 (0.00 to 6.82)	38 more per 1000 (from 17 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Ozenoxacin[11] - clinical success (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	169/357 (47.3%)	111/354 (31.4%)	RR 1.51 (1.25 to 1.82)	160 more per 1000 (from 78 more to 257 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Ozenoxacin[11] - clinical failure (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[13]	none	188/357 (52.7%)	243/354 (68.6%)	RR 0.77 (0.68 to 0.87)	158 fewer per 1000 (from 89 fewer to 220 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Ozenoxacin[11] - microbiological success (day 3 to 4)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	218/279 (78.1%)	134/271 (49.4%)	RR 1.58 (1.38 to 1.81)	287 more per 1000 (from 188 more to 401 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Ozenoxacin[11] - microbiological failure (day 3 to 4)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	53/271 (19.6%)	122/256 (47.7%)	RR 0.41 (0.31 to 0.54)	281 fewer per 1000 (from 219 fewer to 329 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Ozenoxacin[11] - microbiological success (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[14]	none	237/261 (90.8%)	173/248 (69.8%)	RR 1.30 (1.19 to 1.43)	209 more per 1000 (from 133 more to 300 more)	⊕⊕⊕O MODERATE	CRITICAL
Ozenoxacin[11] - microbiological failure (day 6 to 7)												

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Placebo	Relative (95% CI)	Absolute		
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	24/261 (9.2%)	75/248 (30.2%)	RR 0.30 (0.20 to 0.47)	212 fewer per 1000 (from 160 fewer to 242 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk; NA – not applicable; OR – odds ratio												

[1] Topical antibiotics include: mupirocin - 2% 3 times a day for 7 to 9 days; 2% once daily until cleared or 2% 3 times daily for 10 to 12 days; fusidic acid - 2% 3 times a day; topical retapamulin - 1% 2 times daily for 5 days; bacitracin ointment, 2 times daily (unreported dose or course length)
[2] Koning et al. 2012
[3] Downgraded 1 level - 1 or more studies included were deemed at high risk of bias in 1 or more domains by systematic review authors
[4] Downgraded 1 level - heterogeneity >50%
[5] Not downgraded - 1 study includes a range of skin infections, with a subgroup for impetigo described separately and reported here
[6] Downgraded 1 level - not all topical antibiotics are available in UK
[7] Fusidic acid - 2% 3 times a day
[8] Mupirocin - 2% 3 times a day for 7 to 9 days; 2% once daily until cleared or 2% 3 times daily for 10 to 12 days
[9] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[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] Ozenoxacin 1% cream - participants instructed to apply thin layer (a fingertip unit, approximately 0.5 g) to the affected areas twice daily
[12] Hebert et al. 2018; pooled-analysis of 2 randomised controlled trials (Rosen et al. 2018 and Gropper et al. 2014)
[13] 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
[14] 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 ozenoxacin

3.1.2 Oral antibiotics

The evidence for oral antibiotics compared with other treatments for impetigo comes from 1 systematic review and meta-analysis (Koning et al. 2012). For details of Koning et al. 2012, see the section on study details.

Oral phenoxymethylpenicillin compared with placebo

Oral phenoxymethylpenicillin (40 to 60,000 units/kg/day in 3 doses, unreported duration) was not significantly different to placebo in children with impetigo for cure or improvement at 5 days follow-up (1 RCT, n=38, 16.7% versus 0%, relative risk [RR] 7.74, 95% confidence interval [CI] 0.43 to 140.26; very low quality evidence).

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 5

3.2 Antibiotics compared with other treatment

The evidence for antibiotics compared with other treatments for impetigo comes from 1 systematic review and meta-analysis (Koning et al. 2012). For details of Koning et al. 2012, see the section on study details.

3.2.1 Topical antibiotic compared with antiseptic

Topical fusidic acid compared with hydrogen peroxide

A systematic review (Koning et al. 2012) found that topical fusidic acid (2% twice to three times a day for up to 21 days) was not significantly different to hydrogen peroxide cream (1% twice to three times a day for up to 21 days) in children with impetigo for cure or improvement (follow-up not reported; 1 RCT, n=256, 82.0% versus 71.9%, RR 1.14, 95% CI 1.00 to 1.31; moderate quality evidence).

There was no significant difference between topical fusidic acid and hydrogen peroxide in the number of children experiencing adverse events leading to withdrawal (1 RCT, n=256, 2.3% versus 0%, RR 7.00, 95% CI 0.37 to 134.16; low quality evidence) or the number of children with mild side effects (1 RCT, n=256, 7.0% versus 10.2%, RR 0.69, 95% CI 0.31 to 1.56; low quality evidence).

See GRADE profiles: Table 6

3.2.2 Topical antibiotic compared with topical steroid

Topical gentamicin compared with topical betamethasone valerate

A systematic review (Koning et al. 2012) found that topical gentamicin cream (applied three times a day) was not significantly different to topical betamethasone valerate cream (applied three times a day) in people with secondary impetigo (age not reported) for cure or improvement at 3 weeks follow-up (1 RCT, n=54, 29.6% versus 55.6%, RR 0.53, 95% CI 0.27 to 1.04; moderate quality evidence).

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 7

3.2.3 Topical antibiotic plus topical steroid compared with topical steroid

Topical gentamicin plus topical betamethasone valerate compared with betamethasone valerate

A systematic review (Koning et al. 2012) found that topical gentamicin plus betamethasone valerate cream applied three times a day was not significantly different to topical betamethasone valerate alone in people with secondary impetigo (age not reported) for cure or improvement at 3 weeks follow-up (1 RCT, n=52, 72.0% versus 55.6%, RR 1.30, 95% CI 0.85 to 1.97; moderate quality evidence). All topical agents were applied 3 times a day.

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 8

3.2.4 Topical antibiotic compared with antifungal

Topical mupirocin compared with topical terbinafine

A systematic review (Koning et al. 2012) found that topical mupirocin (2% three times a day for 10 days) was not significantly different to topical terbinafine (1% three times a day for 10 days) in children with impetigo for cure or improvement at 10 days

follow-up (1 RCT, n=62, 80.6% versus 58.1%, RR 1.39, 95% CI 0.98 to 1.96; low quality evidence).

There was also no significant difference between topical mupirocin and topical terbinafine for the incidence of adverse events, including burning, stinging, itching or rash (1 RCT, n=62, 3.2% versus 6.5%, RR 0.50, 95% CI 0.05 to 5.23; very low quality evidence).

See GRADE profiles: Table 9

3.3 Choice of antibiotics

3.3.1 Topical antibiotics

The evidence for topical antibiotics compared with other topical antibiotics for impetigo comes from 1 systematic review and meta-analysis (Koning et al. 2012). For details of Koning et al. 2012, see the section on study details.

Topical mupirocin compared with topical fusidic acid

Topical mupirocin (2% twice to three times day for 6 to 8 days) was not significantly different to topical fusidic acid (2% three times a day for up to 8 days) in adults, young people and children with impetigo for cure or improvement at 6 to 8 days follow-up (4 RCTs, n=440, 84.3% versus 85.3%, relative risk [RR] 1.03, 95% confidence interval [CI] 0.95 to 1.11; moderate quality evidence).

Topical mupirocin was associated with significantly more skin reactions compared with topical fusidic acid in people with a range of bacterial skin infections, including impetigo (3 RCTs, n=945, 4.2% versus 1.4%, RR 3.25, 95% CI 1.37 to 7.70 [NICE analysis], number needed to harm [NNH] 36, 95% CI 21 to 138; moderate quality evidence).

See GRADE profiles: Table 10

Topical mupirocin compared with topical neomycin

Topical mupirocin (2% twice a day for 10 to 11 days) was not significantly different to topical neomycin (1% twice a day for 10 to 11 days) in children and young people with impetigo for cure or improvement (follow-up not reported; 1 RCT, n=32, 100% versus 76.5%, RR 1.29, 95% CI 0.98 to 1.71; low quality evidence).

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 11

Topical mupirocin compared with topical polymyxin B/neomycin

Topical mupirocin (2% three times a day for 7 days) was not significantly different to topical polymyxin B/neomycin (three times a day for 7 days) in people with impetigo (age not reported) for cure or improvement at 7 days follow-up (1 RCT, n=8, 100% versus 83.3%, RR 1.06, 95% CI 0.56 to 2.01; very low quality evidence).

There was also no significant difference between topical mupirocin and topical polymyxin B/neomycin for the incidence of rash in people with a range of bacterial skin infections, including impetigo (1 RCT, n=50, 0% versus 3.8%, RR 0.35, 95% CI 0.01 to 8.93; very low quality evidence).

See GRADE profiles: Table 12

Topical fusidic acid compared with topical neomycin/bacitracin

Topical fusidic acid (2% three times a day for 10 days) was more effective than topical neomycin/bacitracin (0.5% three times a day, unreported duration) in newborn babies (aged 3 to 14 days) with bullous impetigo for cure or improvement at 7 days follow-up (1 RCT, n=24, 83.3% versus 8.3%, RR 10.0, 95% CI 1.51 to 66.43, number needed to treat [NNT] 2, 95% CI 1 to 3; very low quality evidence).

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 13

Topical gentamicin compared with topical neomycin

Topical gentamicin (1% three times a day, unreported duration) was more effective than topical neomycin (0.5% three times a day, unreported duration) in adults, young people and children with impetigo for cure or improvement at 7 days follow-up (1 RCT, n=128, 71.4% versus 50.0%, RR 1.43, 95% CI 1.03 to 1.98, NNT 5, 95% CI 3 to 27; very low quality evidence).

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 14

3.3.2 Oral antibiotics

The evidence for oral antibiotics compared with other oral antibiotics for impetigo comes from 1 systematic review and meta-analysis (Koning et al. 2012). For details of Koning et al. 2012, see the section on study details.

Oral macrolides compared with oral penicillins – overall analysis

Oral macrolides were not significantly different to oral penicillins in adults, young people and children with impetigo for cure or improvement at 5 to 16 days follow-up (7 RCTs, n=363, 89.1% versus 85.3%, relative risk [RR] 1.06, 95% confidence interval [CI] 0.98 to 1.15; low quality evidence).

Oral macrolides included erythromycin (30 to 40 mg/kg/day in three to four doses for 10 days), azithromycin (250 mg twice a day [day 1] and once a day [day 2 to 5] for 5 days; or 10 mg/kg/day [max. 500mg] in one dose for 3 days), or clindamycin (150 mg 4 times a day or 300 mg twice a day).

Oral penicillins included phenoxymethylpenicillin (40 to 50 mg/kg/day in three to four doses for 10 days), dicloxacillin (25 mg/kg/day in four doses for 10 days), amoxicillin (50 mg/kg/day for 7 days), cloxacillin (500 mg 4 times a day for 7 days), dicloxacillin/flucloxacillin (12.5 to 25 mg/kg/day and 500 to 3000 mg/day in four doses for 7 days) or dicloxacillin (250 mg four times a day).

No safety or tolerability outcomes were reported for the overall analysis.

See GRADE profiles: Table 15

Oral erythromycin compared with oral phenoxymethylpenicillin

Oral erythromycin (30 to 40 mg/kg/day in three to four doses for 10 days) was more effective than phenoxymethylpenicillin (40 to 50 mg/kg/day in three to four doses for 10 days) in children with impetigo for cure or improvement at 7 to 10 days follow-up (2 RCTs, n=79, 97.4% versus 75.0%, RR 1.29, 95% CI 1.07 to 1.56, number needed to treat [NNT] 5, 95% CI 3 to 13; low quality evidence).

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 15

Oral erythromycin compared with oral amoxicillin

Oral erythromycin (30 mg/kg for 7 days) was not significantly different to oral amoxicillin (50 mg/kg/day for 7 days) in children with impetigo for cure or improvement at 7 days follow-up (1 RCT, n=129, 89.2% versus 89.1%, RR 1.00, 95% CI 0.89 to 1.13; moderate quality evidence).

Oral erythromycin was associated with significantly more children reporting diarrhoea compared with oral amoxicillin (1 RCT, n=129, 16.9% versus 3.1%, RR 5.42, 95% CI 1.25 to 23.47, number needed to harm [NNH] 8, 95% CI 4 to 26; low quality evidence).

See GRADE profiles: Table 15

Oral azithromycin compared with oral erythromycin

Oral azithromycin (250 mg twice on day 1 and once a day for days 2 to 5, for 5 days total) was not significantly different to oral erythromycin (500 mg 4 times a day for 7 days) in adults, young people and children with impetigo for cure or improvement at 11 to 16 days follow-up (1 RCT, n=66, 80.0% versus 67.7%, RR 1.18, 95% CI 0.88 to 1.58; low quality evidence).

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 16

Oral co-amoxiclav compared with oral amoxicillin

Oral co-amoxiclav (40/10 mg/kg/day in three doses for 10 days) was more effective than oral amoxicillin (40 mg/kg/day in three doses for 10 days) in children and young people with impetigo for cure or improvement at 5 days follow-up (1 RCT, n=44, 95.5% versus 68.2%, RR 1.40, 95% CI 1.04 to 1.89, NNT 4, 95% CI 2 to 17; low quality evidence).

There was no significant difference between oral co-amoxiclav and oral amoxicillin in the number of reports of vomiting or diarrhoea (1 RCT, n=44, 0% versus 9.1%, RR 0.20, 95% CI 0.01 to 3.94; very low quality evidence).

See GRADE profiles: Table 17

Oral cefalexin compared with oral cefadroxil

Oral cefalexin (30 mg/kg/day [max 1 g] in two doses for 10 days) was not significantly different to oral cefadroxil (30 mg/kg/day [max 1 g] in one dose for 10 days) in children and young people with impetigo for cure or improvement at 14 days follow-

up (1 RCT, n=96, 91.1% versus 92.2%, RR 0.99, 95% CI 0.88 to 1.12; moderate quality evidence).

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 18

Oral cefalexin compared with oral phenoxymethylpenicillin

Oral cefalexin (40 to 50 mg/kg/day in 3 daily doses for 10 days) was more effective than oral phenoxymethylpenicillin (40 to 50 mg/kg/day in 3 daily doses for 10 days) in children with impetigo for cure or improvement at 8 to 10 days follow-up (1 RCT, n=48, 100% versus 76.0%, RR 1.31, 95% CI 1.04 to 1.64, NNT 5, 95% CI 3 to 14; moderate quality evidence).

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 19

Oral cefalexin compared with oral erythromycin

Oral cefalexin (40 to 50 mg/kg/day in three doses for 10 days) was not significantly different to oral erythromycin (30 to 50 mg/kg/day in three doses for 10 days) in children with impetigo for cure or improvement at 8 to 10 days follow-up (1 RCT, n=48, 100% versus 96.0%, RR 1.04, 95% CI 0.93 to 1.16; high quality evidence).

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 20

Oral cefalexin compared with oral azithromycin

Oral cefalexin (500 mg twice a day for 10 days) was not significantly different to oral azithromycin (500 mg on day 1, 250 mg for days 2 to 5, for 5 days total) in adults with impetigo for cure or improvement at 11 days follow-up (1 RCT, n=18, 75.0% versus 50.0%, RR 1.50, 95% CI 0.72 to 3.14; very low quality evidence).

There was no significant difference between oral cefalexin and oral azithromycin in adults with a range of bacterial skin infections, including impetigo, for incidence of gastrointestinal adverse events (1 RCT, n=366, 16.5% versus 10.9%, RR 1.62, 95% CI 0.88 to 2.97; very low quality evidence).

See GRADE profiles: Table 21

Oral cefaclor compared with oral azithromycin

Oral cefaclor (20 mg/kg/day in one dose for 10 days) was not significantly different to oral azithromycin (10 mg/kg/day in one dose for 3 days) in children with impetigo for cure or improvement at 10 to 14 days follow-up (1 RCT, n=95, 96.1% versus 93.2%; RR 1.03, 95% CI 0.94 to 1.14; moderate quality evidence).

There was no significant difference between oral cefaclor and oral azithromycin in children with a range of bacterial skin infections, including impetigo, for incidence of mild skin side effects (1 RCT, n=200, 2.0% versus 3.0%, RR 0.67, 95% CI 0.11 to 3.90; very low quality evidence).

See GRADE profiles: Table 22

Oral cefaclor compared with oral co-amoxiclav

Oral cefaclor (20 mg/kg/day in three doses, unreported duration) was not significantly different to oral co-amoxiclav (125/30, dose equivalent to 20 mg amoxicillin/kg/day in three doses for 10 days) in children with impetigo for cure or improvement at 10 days follow-up (1 RCT, n=34, 81.3% versus 88.9%, RR 0.91, 95% CI 0.69 to 1.22; moderate quality evidence).

There was no significant difference between oral cefaclor and oral co-amoxiclav in children with a range of bacterial skin infections, including impetigo, for incidence of mild diarrhoea (1 RCT, n=366, 10.9% versus 16.5%, RR 0.66, 95% CI 0.39 to 1.12; low quality evidence).

See GRADE profiles: Table 23

Oral cefadroxil compared with oral flucloxacillin

Oral cefadroxil (40 mg/kg/day for 10 days) was not significantly different to oral flucloxacillin (tablets 750 mg twice a day or suspension 30 to 50 mg/kg/day in two to three doses for 10 days) in adults, young people and children for cure or improvement at 10 to 12 days follow-up (1 RCT, n=60, 75.8% versus 92.6%, RR 0.82, 95% CI 0.66 to 1.02; low quality evidence).

Oral cefadroxil was associated with significantly more incidences of severe adverse events (including stomach ache, rash, fever and vomiting) compared with oral flucloxacillin in people with a range of bacterial skin infections, including impetigo (1 RCT, n=561, 4.3% versus 0.85%, RR 5.01, 95% CI 1.15 to 21.83, NNH 30, 95% CI 16 to 106; very low quality evidence). However, oral cefadroxil was also associated with significantly fewer incidences of diarrhoea compared with oral flucloxacillin in the same population (1 RCT, n=561, 4.3% versus 26.9%, RR 0.16, 95% CI 0.09 to 0.27, NNH 5, 95% CI 3 to 5; low quality evidence).

See GRADE profiles: Table 24

3.3.3 Dual antibiotics

The evidence for a combination of oral plus topical antibiotics compared with topical antibiotics alone for impetigo comes from 1 systematic review and meta-analysis (Koning et al. 2012). For details of Koning et al. 2012, see the section on study details.

Oral cefdinir plus topical tetracycline compared with topical tetracycline

A systematic review (Koning et al. 2012) found that dual therapy with oral cefdinir (9 mg/kg/day) plus topical tetracycline (3% three times a day) for 7 days was not significantly different to monotherapy with topical tetracycline (3% three times a day) for 7 days in children with impetigo for cure at 7 days follow-up (1 RCT, n=34, 50.0% versus 78.6%, RR 0.64, 95% CI 0.28 to 1.45; very low quality evidence).

No safety or tolerability outcomes were reported.

See GRADE profiles**:** Table 25

Oral minomycin plus topical tetracycline compared with topical tetracycline

A systematic review (Koning et al. 2012) found that dual therapy with oral minomycin (4 mg/kg/day) plus topical tetracycline (3% three times a day) for 7 days was not

significantly different to monotherapy with topical tetracycline (3% three times a day) for 7 days in children with impetigo for cure at 7 days follow-up (1 RCT, n=33, 100% versus 78.6%, RR 1.18, 95% CI 0.87 to 1.61; very low quality evidence).

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 25

Oral fosfomycin plus topical tetracycline compared with topical tetracycline

A systematic review (Koning et al. 2012) found that dual therapy with oral fosfomycin (40 mg/kg/day) plus topical tetracycline (3% three times a day) for 7 days was not significantly different to monotherapy with topical tetracycline (3% three times a day) for 7 days in children with impetigo for cure at 7 days follow-up (1 RCT, n=38, 60.0% versus 78.6%, RR 0.76, 95% CI 0.44 to 1.31; very low quality evidence).

No safety or tolerability outcomes were reported.

See GRADE profiles**:** Table 25

3.4 Antibiotic course length

The evidence for antibiotic course length comes from 1 randomised controlled trial (Bowen et al. 2014 [non-inferiority trial; n=508]). Indigenous Australian children aged 4 to 10 years with diagnosis of mild or moderate non-bullous impetigo as judged by a nurse were included. Treatment success at day 7 was the primary outcome, defined as impetigo which had healed or improved.

3.4.1 Shorter course antibiotics compared with longer course antibiotics

3 day course oral co-trimoxazole compared with 5 day course oral co-trimoxazole

A non-inferiority trial (Bowen et al. 2014) compared a 3 day course of oral co-trimoxazole to a 5 day course of oral co-trimoxazole in children with impetigo. The analysis was performed by NICE based on raw data,because absolute differences were not reported and the non-inferiority margin was not applicable to the comparisons reported here.

A 3 day course of oral co-trimoxazole was not significantly different to a 5 day course of oral co-trimoxazole in children with impetigo for the following outcomes: treatment success in intention to treat analysis (1 RCT, n=334, 85.0% versus 84.5%, relative risk [RR] 1.01, 95% confidence interval [CI] 0.92 to 1.10; moderate quality evidence), clinical success (1 RCT, n=334, 98.8% versus 100%, RR 0.99, 95% CI 0.97 to 1.01; moderate quality evidence) and resolution of sores from whole body (1 RCT, n=333, 87.9% versus 90.0%, RR 0.98, 95% CI 0.91 to 1.05; moderate quality evidence).

The antibiotics included in the analysis were: a 3 day course of oral co-trimoxazole (4 mg/kg plus 20 mg/kg [maximum 160 mg plus 800 mg] twice daily) and a 5 day course of oral co-trimoxazole (8 mg/kg plus 40 mg/kg [maximum 320 mg plus 1600 mg] once daily).

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 26

3.5 Antibiotic route of administration

The evidence for route of administration of antibiotics for impetigo comes from 1 systematic review and meta-analysis (Koning et al. 2012), and 2 RCTs Al-Samman et al. 2014 (n=52) and Bowen et al. 2014 (non-inferiority trial; n=508).

For details of Koning et al. 2012, see the section on study details.

Al-Samman et al. 2014 included children aged 2 to 9 years, with a clinical diagnosis of impetigo made by a medical professional. Only children with moderate non-bullous impetigo with between 11 and 20 lesions were included. Parents of children in both intervention and control groups were instructed to wash skin lesions with antibacterial soap and apply fusidic acid and hydrocortisone combination cream as adjuvant therapy. Treatment success at day 8 was the primary outcome, defined as impetigo which was cured (complete absence or only dry lesions without crusts) or improved (a decline in affected area or number of lesions with reduction of signs and symptoms of infection).

Bowen et al. 2014 is a non-inferiority RCT which included children aged 4 to 10 years, with clinical diagnosis of mild to moderate impetigo made by a community nurse. Only Indigenous Australian children were included. Treatment success at day 7 was the primary outcome, defined as impetigo which had healed or improved.

3.5.1 Topical antibiotic compared with oral antibiotic

Topical mupirocin compared with oral erythromycin

A systematic review (Koning et al. 2012) found that topical mupirocin was not significantly different to oral erythromycin in adults, young people and children for cure or improvement at 4 to 12 days follow-up (10 RCTs, n=581, 90.6% versus 85.5%, RR 1.06, 95% CI 1.00 to 1.13; moderate quality evidence; NICE analysis of event rates and total participants reported in Koning et al. 2012). This result was also not significantly different when only including observer blinded studies (2 RCTs, n=137, 95.6% versus 82.6%, RR 1.12, 95% CI 0.86 to 1.46; very low quality evidence).

Topical mupirocin was associated with significantly fewer gastrointestinal adverse events compared with oral erythromycin (4 RCTs, n=297, 5.3% versus 19.3%, RR 0.30, 95% CI 0.14 to 0.60, number needed to harm [NNH] 8, 95% CI 4 to 14; NICE analysis; moderate quality evidence).

Antibiotics included in the analysis were: topical mupirocin (2% three times a day for 5 to 10 days) and oral erythromycin (30 to 50 mg/kg/day in two to four daily doses for 7 to 10 days; 250 mg four times a day for 7 days; or unreported dose).

See GRADE profiles**:** Table 27

Topical mupirocin compared with oral cefalexin

A systematic review (Koning et al. 2012) found that topical mupirocin (2% three times a day for 5 to 10 days) was not significantly different to oral cefalexin (50 mg/kg/day in three doses for 10 days or 250 mg four times a day for 10 days) in children with impetigo for cure or improvement at 8 to 10 days follow-up (1 RCT, n=17, 85.7% versus 90.0%, RR 0.95, 95% CI 0.66 to 1.37; very low quality evidence).

In adults, young people and children with secondary impetigo from infected eczema, there was also no significant difference between topical mupirocin and oral cefalexin (1 RCT, n=159, 63.4% versus 57.1%, RR 1.11, 95% CI 0.86 to 1.43; low quality evidence).

There was no significant difference between topical mupirocin and oral cefalexin in the incidence of diarrhoea (1 RCT, n=159, 2.4% versus 3.9%, RR 0.63, 95% CI 0.11 to 3.65; very low quality evidence).

See GRADE profiles: Table 27

Topical mupirocin compared with oral ampicillin

A systematic review (Koning et al. 2012) found that topical mupirocin (2% three times a day for 5 to 10 days) was not significantly different to oral ampicillin (50 mg four times a day for 5 to 10 days) in people with impetigo (age not reported) for cure or improvement at 10 days follow-up (1 RCT, n=13, 88.9% versus 50.0%, RR 1.78, 95% CI 0.65 to 4.87; very low quality evidence).

No safety or tolerability data was reported.

See GRADE profiles: Table 27

Topical fusidic acid compared with oral erythromycin

A systematic review (Koning et al. 2012) found that topical fusidic acid (2% three times a day for 10 days) was not significantly different to oral erythromycin (50 mg/kg/day in four doses for 10 days) in newborn babies (aged 3 to 14 days) with bullous impetigo, for cure or improvement at 7 days follow-up (1 RCT, n=24, 83.3% versus 58.3%, RR 1.43, 95% CI 0.83 to 2.45; low quality evidence).

No safety or tolerability data was reported.

See GRADE profiles: Table 27

Topical neomycin/bacitracin compared with oral erythromycin

A systematic review (Koning et al. 2012) found that topical neomycin/bacitracin (unreported dose, three times a day for 10 days) was less effective than oral erythromycin (50 mg/kg/day in four doses for 10 days) in newborn babies (aged 3 to 14 days) with bullous impetigo for cure or improvement at 7 days follow-up (1 RCT, n=24, 8.3% versus 58.3%, RR 0.14, 95% CI 0.02 to 0.99, NNT 2, 95% CI 2 to 5; very low quality evidence).

No safety or tolerability data was reported.

See GRADE profiles: Table 27

Topical chloramphenicol compared with oral erythromycin

A systematic review (Koning et al. 2012) found that topical chloramphenicol (unreported dose, 3 times a day for 10 days) was not significantly different to oral erythromycin (50 mg/kg/day in four doses for 10 days) in newborn babies (aged 3 to 14 days) with bullous impetigo for cure or improvement at 7 days follow-up (1 RCT, n=24, 16.7% versus 58.3%, RR 0.29, 95% CI 0.07 to 1.10; low quality evidence).

No safety or tolerability data was reported.

See GRADE profiles: Table 27

3.5.2 Intramuscular antibiotic compared with oral antibiotic

Intramuscular ceftriaxone compared with oral cefadroxil

An RCT (Al-Samman et al. 2014) found that intramuscular ceftriaxone (single injection 50 mg/kg) was not significantly different to oral cefadroxil (30 mg/kg/day twice a day for 7 days) in children with impetigo for cure at day 8 (1 RCT, n=49, 100% versus 100%, relative risk [RR] 1.00, 95% confidence interval [CI] 0.93 to 1.08; moderate quality evidence), cure at day 3 (1 RCT, n=49, 88.0% versus 83.3%, RR 1.06, 95% CI 0.84 to 1.33; low quality evidence), improved response rate at day 3, failure to respond at day 3 or relapse within 1 month.

No safety or tolerability outcomes were reported.

See GRADE profiles: Table 28

Intramuscular benzylpenicillin compared with oral co-trimoxazole

A non-inferiority RCT (Bowen et al. 2014) found that at a non-inferiority margin of 10%, oral co-trimoxazole was non-inferior to intramuscular benzylpenicillin in children with impetigo for the following outcomes: treatment success at day 7 in intention to treat analysis (1 RCT, n=490, 85.3% versus 84.7%, RR 1.01, 95% CI 0.93 to 1.09; moderate quality evidence), clinical success at day 7 (1 RCT, n=490, 98.7% versus 99.4%, RR 0.99, 95% CI 0.97 to 1.01; moderate quality evidence) and the resolution of sores from whole body at day 7 (1 RCT, n=488, 85.2% versus 88.9%, RR 0.96, 95% CI 0.89 to 1.03; low quality evidence).

Intramuscular benzylpenicillin was associated with significantly more reports of adverse events compared with oral co-trimoxazole (1 RCT, n=503, 30.6% versus 1.5%, RR 21.01, 95% CI 8.53 to 51.27, NNH 4, 95% CI 2 to 4; NICE analysis based on raw data as absolute difference not reported and non-inferiority margin not applicable to this outcome; low quality evidence).

Antibiotics included in analysis were: oral co-trimoxazole (4 mg/kg plus 20 mg/kg [maximum 160 mg plus 800 mg] twice a day for 3 days; or, 8 mg/kg plus 40 mg/kg [maximum 320 mg plus 1600 mg] once a day for 5 days) and intramuscular benzylpenicillin (weight-banded intramuscular injection into the thigh or buttock [weight band </=6 kg, dose 225 mg; 6.1 to 10 kg, 337.5 mg; 10.1 to 15 kg, 450 mg; 15.1 to 20 kg, 675 mg; >20 kg, 900 mg]).

See GRADE profiles: Table 29

4 Terms used in the guideline

4.1 Non-bullous impetigo

Impetigo characterised by thin-walled vesicles or pustules which rupture quickly, forming a golden-brown crust (NICE clinical knowledge summaries on impetigo).

4.2 Bullous impetigo

Impetigo characterised by the presence of fluid-filled vesicles and blisters often with a diameter of over 1 cm which rupture, leaving a thin, flat, yellow-brown crust (NICE clinical knowledge summaries on impetigo).

4.3 Decolonisation

Use of topical treatments (antiseptic body wash, nasal ointment or a combination of both) and personal hygiene measures to remove the bacteria causing the infection from the body (NICE clinical knowledge summaries on boils, carbuncles and staphylococcal carriage).

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 – impetigo, 2018 • British Skin Foundation - impetigo • Elliot et al. 2006 • Hartman-Adams et al. 2014 • Koning et al. 2012 • Public Health England – antibiotic guidance for primary care • 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)
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)?	• Clinical Knowledge Summary – impetigo, 2018 • NICE guideline NG63: antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • NICE guideline NG51: sepsis: recognition, diagnosis and early management (2016, updated 2017) • NICE guideline CG160: fever in under 5s: assessment and initial management (2013, updated 2017) • Clinical Knowledge Summary – diarrhoea – antibiotic associated, 2018

Key area	Key question(s)	Evidence sources
		• NICE guideline CG183: drug allergy: diagnosis and management (2014) • British National Formulary, July 2019 • Committee experience
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection • What is the need for broad or narrow spectrum antimicrobials? • What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	• NICE guideline NG15: antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • Chief medical officer (CMO) report (2011) • ESPAUR report (2018)
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• NHSBSA Drug Tariff
Regulatory status	• What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics
Antimicrobial prescribing strategies	• What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review – see appendix F for included studies
Antimicrobials	• Which people are most likely to benefit from an antimicrobial?	• Evidence review – see appendix F for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)?	• Evidence review – see appendix F for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review – see appendix F for included studies • British National Formulary, July 2019

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

Appendix B: Review protocol

Field (based on PRISMA-P	Content
Review question	What antimicrobial interventions are effective in managing impetigo?
Types of review question	Intervention.
Objective of the review	To determine the effectiveness of antimicrobial prescribing interventions in managing impetigo to address antimicrobial resistance. In line with the major goals of antimicrobial stewardship this includes interventions that lead prescribers to: • optimise therapy for individuals • reduce overuse, misuse or abuse of antimicrobials All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.
Eligibility criteria – population/ disease/ condition/ issue/domain	Population: Adults and children (aged 72 hours and older) with impetigo of any severity.
Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	The review will include studies which include: • Antimicrobial pharmacological interventions[1]. For the treatment or prevention of impetigo 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).

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

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Eligibility criteria – comparator(s)/ control or reference (gold) standard	Any other plausible strategy or comparator, including: • Placebo or no treatment. • Non-pharmacological interventions. • Non-antimicrobial pharmacological interventions. • Other antimicrobial pharmacological interventions.
Outcomes and prioritisation	a) Infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) b) Time to clinical cure (mean or median time to resolution of illness) c) Reduction in symptoms (duration or severity) d) Rate of complications with or without treatment e) Recurrence of impetigo f) Rate of complications g) Safety, tolerability, and adverse effects. h) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. i) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. j) Service user experience. k) Health and social care related quality of life. l) Health and social care utilisation (including length of stay, planned and unplanned contacts). The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).

Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If no systematic review or RCT evidence is available progress to: • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Cohort studies • Pre and post intervention studies (before and after) • 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). • Studies that include pharmacological preparations which are not licensed in the UK will be included, but will only be prioritised for inclusion in the review when: o There are no other studies that include preparations with a UK licence within that antibiotic class, or o the preparations that are not licensed in the UK are proposed to have a similar efficacy or mechanism of action to preparations that are licensed in the UK
Proposed sensitivity/ sub-group analysis, or meta-regression	The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). These will be analysed within these categories to enable the production of management recommendations.

Selection process – duplicate screening/ selection/ analysis	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved. If large numbers of papers are identified and included at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.
Data management (software)	Data management will be undertaken using EPPI-reviewer software. Any pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following sources will be searched : • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cochrane Database of Systematic Reviews (CDSR) via Wiley • Database of Abstracts of Effectiveness (DARE) via Wiley – legacy database, last updated April 2015 • Embase via Ovid • Health Technology Assessment (HTA) via Wiley • MEDLINE via Ovid • MEDLINE-in-Process (including Daily Update and Epub Ahead of Print) via **Ovid** The search strategy will be developed in MEDLINE and then adapted or translated as appropriate for the other sources, taking into account their size, search functionality and subject coverage. A summary of the proposed search strategy is given in the appendix below. Database functionality will be used, where available, to exclude:

	• non-English language papers • animal studies • editorials, letters, news items, case reports and commentaries • conference abstracts and posters • theses and dissertations • duplicates. Date limits will be applied to restrict the search results to: • studies published from 2000 to the present day The results will be downloaded in the following sets: • Systematic reviews and meta analysis • Randomised controlled trials • Observational and comparative studies • Other results Duplicates will be removed using automated and manual processes. The de-duplicated file will be uploaded into EPPI-Reviewer for data screening. See Appendix for details of search terms to be used.
Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-ng10050/consultation/html-content Email: infections@nice.org.uk
Highlight if amendment to previous protocol	For details please see the interim process guide (2017).
Search strategy – for one database	For details see appendix C.
Data collection process – forms/duplicate	GRADE profiles will be used, for details see appendix H.

Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix H.
Methods for assessing bias at outcome/ study level	Standard study checklists were used to critically appraise individual studies. For details please see the interim process guide (2017). The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see the interim process guide (2017).
Methods for analysis – combining studies and exploring (in)consistency	For details please see the interim process guide (2017).
Meta-bias assessment – publication bias, selective reporting bias	For details please see the interim process guide (2017).
Assessment of confidence in cumulative evidence	For details please see the interim process guide (2017).
Rationale/ context – Current management	For details please see the interim process guide (2017).
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the interim process guide (2017). Staff from NICE undertook systematic literature searches, appraised the evidence and conducted meta-analysis where appropriate. The

	guideline was drafted 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

1 Impetigo/ (1227)

2 Soft Tissue Infections/ (3265)

3 Pyoderma/ (2534)

4 impetigo*.ti,ab. (1290)

5 or/1-4 (7490)

6 Amikacin/ (3939)

7 Amikacin*.ti,ab. (7842)

8 exp Amoxicillin/ (10678)

9 Amoxicillin*.ti,ab. (12160)

10 Ampicillin/ (13181)

11 Ampicillin*.ti,ab. (20061)

12 Azithromycin/ (4651)

13 (Azithromycin* or Azithromicin* or Zithromax*).ti,ab. (6384)

14 Penicillin G/ (8959)

15 (Benzylpenicillin* or "Penicillin G").ti,ab. (7587)

16 (Ceftaroline* or Zinforo*).ti,ab. (493)

17 Clarithromycin/ (5944)

18 (Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab. (7742)

19 Chloramphenicol/ (19151)

20 (Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab. (24304)

21 Clindamycin/ (5496)

22 (Clindamycin* or Dalacin* or Zindaclin*).ti,ab. (8945)

23 Amoxicillin-Potassium Clavulanate Combination/ (2423)

24 (Co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab. (12953)

25 Doxycycline/ (9074)

26 (Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab. (11046)

27 (Ertapenem* or Invanz*).ti,ab. (1143)

28 Erythromycin/ (13549)

29 Erythromycin Estolate/ (148)

30 Erythromycin Ethylsuccinate/ (514)

31 (Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab. (18820)

32 Floxacillin/ (705)

33 (Floxacillin* or Flucloxacillin*).ti,ab. (739)

34 Framycetin/ (495)

35 Framycetin*.ti,ab. (146)
36 Fusidic Acid/ (1562)
37 ("Fusidic acid" or fusidate* or Fucidin*).ti,ab. (1828)
38 Gentamicins/ (17757)
39 (Gentamicin* or Gentamycin* or Cidomycin*).ti,ab. (23543)
40 Imipenem/ (3888)
41 (Imipenem* or Primaxin*).ti,ab. (8701)
42 Levamisole/ (4249)
43 (Levamisole* or ergamisol*).ti,ab. (4214)
44 Levofloxacin/ (3018)
45 (Levofloxacin* or Evoxil* or Tavanic*).ti,ab. (6012)
46 Linezolid/ (2681)
47 (Linezolid* or Zyvox*).ti,ab. (4404)
48 Meropenem*.ti,ab. (4645)
49 Metronidazole/ (12224)
50 Metronidazole*.ti,ab. (13196)
51 exp Neomycin/ (9080)
52 (neom?cin* or "Neo-Fradin").ti,ab. (8725)
53 Mupirocin/ (1149)
54 (Mupirocin* or Bactroban*).ti,ab. (1478)
55 Ofloxacin/ (5912)
56 (Ofloxacin* or Tarivid*).ti,ab. (6137)
57 Penicillin V/ (2151)
58 (Phenoxymethylpenicillin* or "Penicillin V").ti,ab. (1421)
59 Piperacillin/ (2639)
60 (Piperacillin* or Tazobactam* or Tazocin*).ti,ab. (6081)
61 (Retapamulin* or Altargo* or Altabax* or Altargo*).ti,ab. (91)
62 Teicoplanin/ (2173)
63 (Teicoplanin* or Targocid*).ti,ab. (3131)
64 Tedizolid*.ti,ab. (164)
65 (Tigecycline* or Tygacil*).ti,ab. (2332)
66 Vancomycin/ (12807)
67 (Vancomycin* or Vancomicin* or Vancocin*).ti,ab. (21825)
68 or/6-67 (229555)
69 5 and 68 (1167)
70 exp Aminoglycosides/ (148610)
71 Aminoglycoside*.ti,ab. (16387)
72 exp Penicillins/ (78462)
73 Penicillin*.ti,ab. (49554)
74 exp beta-Lactamases/ (21398)

75 exp beta-Lactamase inhibitors/ (7347)

76 ((beta adj Lactamase*) or betaLactamase* or beta-Lactamase*).ti,ab. (23080)

77 beta-Lactams/ (6165)

78 (beta-Lactam or betaLactam or beta Lactam or beta-Lactams or betaLactams or beta Lactams).ti,ab. (17822)

79 exp Carbapenems/ (9871)

80 Carbapenem*.ti,ab. (9829)

81 exp Cephalosporins/ (40709)

82 Cephalosporin*.ti,ab. (19084)

83 exp Fluoroquinolones/ (30647)

84 Fluoroquinolone*.ti,ab. (13314)

85 exp Macrolides/ (103337)

86 macrolide*.ti,ab. (13389)

87 Polymyxins/ (2843)

88 Polymyxin*.ti,ab. (6193)

89 exp Quinolones/ (43985)

90 Quinolone*.ti,ab. (11875)

91 exp Tetracyclines/ (46229)

92 Tetracycline*.ti,ab. (31340)

93 or/70-92 (479094)

94 5 and 93 (1284)

95 Chlorhexidine/ (7731)

96 (Chlorhexidine* or Unisept* or Hibiscrub* or Hydrex* or Hibi or HiBiTane*).ti,ab. (8393)

97 ("Dialkylcarbamoyl chloride" or "Cutimed Sorbact").ti,ab. (14)

98 Glucose oxidase/ (4752)

99 "Glucose oxidase".ti,ab. (5211)

100 Hydrogen Peroxide/ (53495)

101 ("Hydrogen peroxide" or crystacide*).ti,ab. (42354)

102 Lactoperoxidase/ (1308)

103 (Lactoperoxidase* or Flaminal*).ti,ab. (2305)

104 (Octenidine* or Octenilin*).ti,ab. (200)

105 (Polihexanide* or Suprasorb* or Polyhexamethylene*).ti,ab. (426)

106 Povidone-Iodine/ (2652)

107 (Povidone-Iodine* or Betadine* or Videne* or Inadine*).ti,ab. (2785)

108 Potassium Permanganate/ (1524)

109 ("Potassium permanganate" or "EN-Potab" or Permitabs).ti,ab. (1357)

110 Proflavine/ (523)

111 Proflavine*.ti,ab. (599)

112 Silver Sulfadiazine/ (900)

113 (Silver Sulfadiazine* or Flamazine*).ti,ab. (784)

114 (reactive oxygen or surgihoney*).ti,ab. (91323)

115 Iodine/ (24439)

116 (Iodine* or Iodoflex* or Iodosorb* or Iodozyme* or Oxyzyme*).ti,ab. (38507)

117 Honey/ (3491)

118 Apitherapy/ (119)

119 (Apitherap* or L-Mesitran or MANUKApli or Medihoney* or Melladerm* or Mesitran*).ti,ab. (80)

120 (honey* adj3 (topical* or local* or ointment* or cream* or skin* or dermatolog* or lotion* or gel* or paste*)).ti,ab. (264)

121 exp anti-infective agents, local/ (216791)

122 (Antiseptic* or anti-septic* or anti septic* or anti-infective* or anti infective* or antiinfective* or microbicide*).ti,ab. (12034)

123 Acetic Acid/ (9491)

124 (vinegar* or acetic acid*).ti,ab. (32358)

125 Sodium Bicarbonate/ (4377)

126 ((bicarbonate* or baking*) adj2 (sodium* or soda*)).ti,ab. (5706)

127 (S-Bicarb* or SodiBic* or Thamicarb* or Polyfusor* or EssCarb*).ti,ab. (3)

128 ((alkaliser* or alkalizer* or alkalinisation* or alkalinization* or alkalinising or alkalinizing) adj3 (drug* or agent* or therap*)).ti,ab. (181)

129 Magnesium Sulfate/ (4917)

130 ((Magnesium* or Epsom*) adj2 (sulfate* or sulphate* or salt*)).ti,ab. (4937)

131 or/95-130 (402484)

132 5 and 131 (223)

133 watchful waiting/ (2916)

134 "no intervention*".ti,ab. (6087)

135 (watchful* adj2 wait*).ti,ab. (2017)

136 (wait adj2 see).ti,ab. (1175)

137 (expectant* adj2 manage*).ti,ab. (2666)

138 (active* adj2 surveillance*).ti,ab. (5736)

139 (observing or observe or observes or observation or observations).ti,ab. (625880)

140 or/133-139 (643815)

141 5 and 140 (130)

142 Inappropriate prescribing/ (2395)

143 ((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab. (25331)

144 ((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. (21462)

145 ((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. (91711)

146 or/142-145 (136691)

147 5 and 146 (447)

148 anti-infective agents/ or exp anti-bacterial agents/ (691413)

149 (antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*").ti,ab. (389866)

150 or/148-149 (838856)

151 5 and 150 (3024)

152 69 or 94 or 132 or 141 or 147 or 151 (3305)

153 limit 152 to yr="2000 -Current" (2124)

154 limit 153 to english language (1869)

155 Animals/ not (Animals/ and Humans/) (4487157)

156 154 not 155 (1743)

157 limit 156 to (letter or historical article or comment or editorial or news or case reports) (462)

158 156 not 157 (1281)

159 Meta-Analysis.pt. (94639)

160 Meta-Analysis as Topic/ (16560)

161 Network Meta-Analysis/ (534)

162 Review.pt. (2300835)

163 exp Review Literature as Topic/ (10196)

164 (metaanaly* or metanaly* or (meta adj3 analy*)).ti,ab. (112064)

165 (review* or overview*).ti. (371408)

166 (systematic* adj5 (review* or overview*)).ti,ab. (113069)

167 ((quantitative* or qualitative*) adj5 (review* or overview*)).ti,ab. (7261)

168 ((studies or trial*) adj2 (review* or overview*)).ti,ab. (35006)

169 (integrat* adj3 (research or review* or literature)).ti,ab. (8582)

170 (pool* adj2 (analy* or data)).ti,ab. (22210)

171 (handsearch* or (hand adj3 search*)).ti,ab. (7467)

172 (manual* adj3 search*).ti,ab. (4590)

173 or/159-172 (2505368)

174 158 and 173 (389)

175 69 or 94 or 132 or 141 or 147 (2189)

176 limit 175 to yr="2000 -Current" (1317)

177 limit 176 to english language (1174)

178 Animals/ not (Animals/ and Humans/) (4487157)

179 177 not 178 (1079)

180 limit 179 to (letter or historical article or comment or editorial or news or case reports) (244)

181 179 not 180 (835)
182 Randomized Controlled Trial.pt. (471781)
183 Controlled Clinical Trial.pt. (92751)
184 Clinical Trial.pt. (513060)
185 exp Clinical Trials as Topic/ (319528)
186 Placebos/ (34152)
187 Random Allocation/ (96642)
188 Double-Blind Method/ (148399)
189 Single-Blind Method/ (25951)
190 Cross-Over Studies/ (44098)
191 ((random* or control* or clinical*) adj3 (trial* or stud*)).ti,ab. (963724)
192 (random* adj3 allocat*).ti,ab. (27301)
193 placebo*.ti,ab. (181546)
194 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab. (145741)
195 (crossover* or (cross adj over*)).ti,ab. (68348)
196 or/182-195 (1696821)
197 181 and 196 (214)
198 Observational Studies as Topic/ (3417)
199 Observational Study/ (54953)
200 Epidemiologic Studies/ (7811)
201 exp Case-Control Studies/ (955842)
202 exp Cohort Studies/ (1800760)
203 Cross-Sectional Studies/ (279684)
204 Controlled Before-After Studies/ (363)
205 Historically Controlled Study/ (145)
206 Interrupted Time Series Analysis/ (507)
207 Comparative Study.pt. (1815167)
208 case control*.ti,ab. (100932)
209 case series.ti,ab. (50739)
210 (cohort adj (study or studies)).ti,ab. (137791)
211 cohort analy*.ti,ab. (5533)
212 (follow up adj (study or studies)).ti,ab. (42434)
213 (observational adj (study or studies)).ti,ab. (70620)
214 longitudinal.ti,ab. (179034)
215 prospective.ti,ab. (444529)
216 retrospective.ti,ab. (380436)
217 cross sectional.ti,ab. (239943)
218 or/198-217 (4026048)
219 181 and 218 (365)
220 174 or 197 or 219 (774)

221 158 not 220 (507)

Database name: Embase

Database: Embase <1974 to 2018 Week 48>

Search Strategy:

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1 exp impetigo/ (3468)

2 impetigo*.ti,ab. (1772)

3 pyoderma/ (2306)

4 soft tissue infection/ (10241)

5 or/1-4 (16011)

6 amikacin/ (42587)

7 Amikacin.ti,ab. (12304)

8 amoxicillin/ (58055)

9 Amoxicillin*.ti,ab. (20411)

10 ampicillin/ (79376)

11 Ampicillin*.ti,ab. (26003)

12 azithromycin/ (31349)

13 (Azithromycin* or Azithromicin* or Zithromax*).ti,ab. (11093)

14 penicillin G/ (73254)

15 (Benzylpenicillin* or "Penicillin G").ti,ab. (8852)

16 ceftaroline/ (1139)

17 (Ceftaroline* or Zinforo*).ti,ab. (802)

18 clarithromycin/ (34451)

19 (Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab. (12676)

20 chloramphenicol/ (53809)

21 (Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab. (24033)

22 clindamycin/ (47238)

23 (Clindamycin* or Dalacin* or Zindaclin*).ti,ab. (12693)

24 amoxicillin plus clavulanic acid/ (34790)

25 (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. (19363)

26 doxycycline/ (47791)

27 (Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab. (17242)

28 ertapenem/ (6232)

29 (Ertapenem* or Invanz*).ti,ab. (2143)

30 erythromycin estolate/ or erythromycin ethylsuccinate/ or erythromycin/ (70306)

31 (Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab. (22960)

32 flucloxacillin/ (7896)
33 (Floxacillin* or Flucloxacillin*).ti,ab. (1293)
34 framycetin/ (1373)
35 Framycetin*.ti,ab. (156)
36 fusidic acid/ (7156)
37 ("Fusidic acid" or fusidate* or Fucidin*).ti,ab. (2189)
38 gentamicin/ (98811)
39 (Gentamicin* or Gentamycin* or Cidomycin*).ti,ab. (32133)
40 imipenem/ (34619)
41 (Imipenem* or Primaxin*).ti,ab. (13955)
42 levamisole/ (11610)
43 (Levamisole* or ergamisol*).ti,ab. (5383)
44 levofloxacin/ (31925)
45 (Levofloxacin* or Evoxil* or Tavanic*).ti,ab. (10893)
46 linezolid/ (18019)
47 (Linezolid* or Zyvox*).ti,ab. (7529)
48 meropenem/ (27425)
49 Meropenem*.ti,ab. (9197)
50 metronidazole/ (62595)
51 Metronidazole*.ti,ab. (19813)
52 neomycin/ (19378) Neomycin exploded in medline but maybe embase version doesn't make a difference? (19,378 certainly seems like enough results..)
53 (neom?cin* or "Neo-Fradin").ti,ab. (9111)
54 pseudomonic acid/ (6411)
55 (Mupirocin or Bactroban).ti,ab. (2282)
56 ofloxacin/ (24915)
57 (Ofloxacin* or Tarivid*).ti,ab. (8746)
58 penicillin V/ (6875)
59 (Phenoxymethylpenicillin* or "Penicillin V").ti,ab. (1521)
60 piperacillin/ (18492)
61 (Piperacillin* or Tazobactam* or Tazocin*).ti,ab. (10989)
62 retapamulin/ (344)
63 (Retapamulin* or Altargo* or Altabax* or Altargo*).ti,ab. (141)
64 teicoplanin/ (12917)
65 (Teicoplanin* or Targocid*).ti,ab. (4719)
66 tedizolid/ (507)
67 Tedizolid*.ti,ab. (280)
68 tigecycline/ (8900)
69 (Tigecycline* or Tygacil*).ti,ab. (4050)
70 vancomycin/ (81498)

71 (Vancomycin* or Vancomicin* or Vancocin*).ti,ab. (35005)

72 or/6-71 (557557)

73 5 and 72 (6413)

74 aminoglycoside/ (14881) as above - presumably intention not to explode like medline term

75 Aminoglycoside*.ti,ab. (21924)

76 penicillin derivative/ (30751)

77 Penicillin*.ti,ab. (49834)

78 beta lactamase/ (17942)

79 beta-Lactamase inhibitor/ (4016)

80 ((beta adj Lactamase*) or betaLactamase* or beta-Lactamase*).ti,ab. (30477)

81 *beta-Lactam/ or beta lactam antibiotic/ or *beta lactam derivative/ (22400)

82 (beta-Lactam or betaLactam or beta Lactam or beta-Lactams or betaLactams or beta Lactams).ti,ab. (25339)

83 *carbapenem derivative/ (1633) exploded in medline - presumably focused because of numbers

84 Carbapenem*.ti,ab. (16825)

85 *cephalosporin derivative/ (7399)

86 Cephalosporin*.ti,ab. (27408)

87 *quinolone derivative/ (4952)exploded in medline - presumably focused because of numbers

88 Fluoroquinolone*.ti,ab. (19440)

89 *Macrolide/ (8267)exploded in medline - presumably focused because of numbers

90 Macrolide*.ti,ab. (19178)

91 *Polymyxin/ (3274)exploded in medline - presumably focused because of numbers

92 Polymyxin*.ti,ab. (7018)

93 Quinolone*.ti,ab. (17639) No emtree but from memory because there isn't one in embase for this term?

94 *tetracycline derivative/ (3028)exploded in medline - presumably focused because of numbers

95 Tetracycline*.ti,ab. (35749)

96 or/74-95 (237051)

97 5 and 96 (2620)

98 *chlorhexidine/ (5808) presumably focused because of numbers

99 (Chlorhexidine* or Unisept* or Hibiscrub* or Hydrex* or Hibi or HiBiTane*).ti,ab. (11198)

100 ("Dialkylcarbamoyl chloride" or "Cutimed Sorbact").ti,ab. (23)

101 glucose oxidase/ (6432)

102 "Glucose oxidase".ti,ab. (6760)

103 *hydrogen peroxide/ (20171)

104 ("Hydrogen peroxide" or crystacide*).ti,ab. (55846)

105 lactoperoxidase/ (1623)

106 (Lactoperoxidase* or Flaminal*).ti,ab. (2550)

107 octenidine/ (538)

108 (Octenidine* or Octenilin*).ti,ab. (305)

109 (Polihexanide* or Suprasorb* or Polyhexamethylene*).ti,ab. (632)

110 povidone iodine/ (9478)

111 (Povidone-Iodine* or Betadine* or Videne* or Inadine*).ti,ab. (3996)

112 permanganate potassium/ (2819)

113 ("Potassium permanganate" or "EN-Potab" or Permitabs).ti,ab. (1784)

114 proflavine/ (826)

115 proflavine*.ti,ab. (484)

116 sulfadiazine silver/ (3644)

117 (Silver Sulfadiazine* or Flamazine*).ti,ab. (1168)

118 *reactive oxygen metabolite/ (22729)

119 (reactive oxygen or surgihoney*).ti,ab. (128841)

120 iodine/ (24755)

121 (Iodine* or Iodoflex* or Iodosorb* or Iodozyme* or Oxyzyme*).ti,ab. (51313)

122 honey-based wound dressing/ or honey/ (6070)

123 apitherapy/ (184)

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

125 (honey* adj3 (topical* or local* or ointment* or cream* or skin* or dermatolog* or lotion* or gel* or paste*)).ti,ab. (449)

126 topical antiinfective agent/ (5610)

127 (Antiseptic* or anti-septic* or anti septic* or anti-infective* or anti infective* or antiinfective* or microbicide*).ti,ab. (17856)

128 acetic acid/ (46803)

129 (vinegar* or acetic acid*).ti,ab. (47414)

130 bicarbonate/ (44536)

131 ((bicarbonate* or baking*) adj2 (sodium* or soda*)).ti,ab. (8297)

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

133 ((alkaliser* or alkalizer* or alkalinisation* or alkalinization* or alkalinising or alkalinizing) adj3 (drug* or agent* or therap*)).ti,ab. (259)

134 magnesium sulphate/ (15001)

135 ((Magnesium* or Epsom*) adj2 (sulfate* or sulphate* or salt*)).ti,ab. (7521)

136 or/98-135 (431056)

137 5 and 136 (459)

138 watchful waiting/ (3564)

139 "no intervention*".ti,ab. (9726)

140 (watchful* adj2 wait*).ti,ab. (3486)

141 (wait adj2 see).ti,ab. (1860)

142 (expectant* adj2 manage*).ti,ab. (4349)

143 (active* adj2 surveillance*).ti,ab. (11184)

144 (observing or observe or observes or observation or observations).ti,ab. (858656)

145 or/138-144 (888735)

146 5 and 145 (323)

147 exp Inappropriate prescribing/ (4153)

148 ((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab. (43525)

149 ((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. (41301)

150 ((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. (132611)

151 or/147-150 (214222)

152 5 and 151 (1406)

153 exp *antiinfective agent/ (1189088)

154 (antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*").ti,ab. (563733)

155 or/153-154 (1517219)

156 5 and 155 (7216)

157 73 or 97 or 137 or 146 or 152 or 156 (9433)

158 limit 157 to yr="2000 -Current" (7209)

159 limit 158 to english language (6610)

160 nonhuman/ not (human/ and nonhuman/) (4263490)

161 159 not 160 (6250)

162 (letter or editorial).pt. (1632733)

163 161 not 162 (5840)

164 (conference abstract or conference paper or conference proceeding or "conference review").pt. (3977552)

165 163 not 164 (4740)

166 limit 165 to medline (258)

167 165 not 166 (4482)

168 Systematic Review/ (185505)

169 Meta Analysis/ (152864)

170 Review/ (2297747)

171 Review.pt. (2379069)

172 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (182226)

173 (review$ or overview$).ti. (514051)

174 (systematic$ adj5 (review$ or overview$)).tw. (180456)

175 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (10942)
176 ((studies or trial$) adj2 (review$ or overview$)).tw. (49989)
177 (integrat$ adj3 (research or review$ or literature)).tw. (12186)
178 (pool$ adj2 (analy$ or data)).tw. (38841)
179 (handsearch$ or (hand adj3 search$)).tw. (10315)
180 (manual$ adj3 search$).tw. (6686)
181 or/168-180 (2934516)
182 167 and 181 (1277)
183 73 or 97 or 137 or 146 or 152 (7703)
184 limit 183 to yr="2000 -Current" (6059)
185 limit 184 to english language (5595)
186 nonhuman/ not (human/ and nonhuman/) (4263490)
187 185 not 186 (5304)
188 (letter or editorial).pt. (1632733)
189 187 not 188 (4945)
190 (conference abstract or conference paper or conference proceeding or "conference review").pt. (3977552)
191 189 not 190 (4147)
192 limit 191 to medline (165)
193 191 not 192 (3982)
194 exp Clinical Trial/ (1345740)
195 Randomization/ (80124)
196 Placebo/ (326769)
197 Double Blind Procedure/ (155432)
198 Single Blind Procedure/ (33132)
199 Crossover Procedure/ (57350)
200 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (1510352)
201 (random$ adj3 allocat$).tw. (39459)
202 placebo$.tw. (281124)
203 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (217816)
204 (crossover$ or (cross adj over$)).tw. (96525)
205 or/194-204 (2557875)
206 193 and 205 (856)
207 Clinical study/ (151277)
208 Case control study/ (133738)
209 Family study/ (25029)
210 Longitudinal study/ (118826)
211 Retrospective study/ (711601)
212 comparative study/ (782108)
213 Prospective study/ (485362)

214 Randomized controlled trials/ (153239)
215 213 not 214 (480461)
216 Cohort analysis/ (420196)
217 cohort analy$.tw. (10269)
218 (Cohort adj (study or studies)).tw. (237836)
219 (Case control$ adj (study or studies)).tw. (120451)
220 (follow up adj (study or studies)).tw. (58101)
221 (observational adj (study or studies)).tw. (134811)
222 (epidemiologic$ adj (study or studies)).tw. (97642)
223 (cross sectional adj (study or studies)).tw. (174465)
224 case series.tw. (85728)
225 prospective.tw. (748444)
226 retrospective.tw. (728629)
227 or/207-212,215-226 (3441168)
228 193 and 227 (1055)
229 182 or 206 or 228 (2472)
230 167 not 229 (2010)

Database name: CDSR & CENTRAL
#1 MeSH descriptor: [Impetigo] this term only 85
#2 MeSH descriptor: [Soft Tissue Infections] this term only 105
#3 MeSH descriptor: [Pyoderma] this term only 40
#4 impetigo:ti,ab 168
#5 {or #1-#4} 321
#6 [mh ^Amikacin] 352
#7 Amikacin*:ti,ab 703
#8 [mh Amoxicillin] 2573
#9 amoxicillin*:ti,ab 3429
#10 [mh ^Ampicillin] 989
#11 Ampicillin*:ti,ab 1336
#12 [mh ^Azithromycin] 843
#13 (Azithromycin* or Azithromicin* or Zithromax*):ti,ab 1827
#14 [mh ^"Penicillin G"] 252
#15 (Benzylpenicillin* or "Penicillin G"):ti,ab 349
#16 (Ceftaroline* or Zinforo*):ti,ab 69
#17 [mh ^Clarithromycin] 1335
#18 (Clarithromycin* or Clarie* or Klaricid* or Xetinin*):ti,ab 2361
#19 [mh ^Chloramphenicol] 286
#20 (Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*):ti,ab 437

#21 [mh ^Clindamycin] 832

#22 (Clindamycin* or Dalacin* or Zindaclin*):ti,ab 1315

#23 [mh ^"Amoxicillin-Potassium Clavulanate Combination"] 572

#24 ((Co NEXT amoxiclav*) or Coamoxiclav* or (Amox NEXT clav*) or (Amoxicillin NEXT Clavulanic NEXT Acid*) or (Amoxicillin NEXT Potassium NEXT Clavulanate NEXT Combination*) or (Amoxi NEXT Clavulanate*) or (Clavulanate NEXT Potentiated NEXT Amoxycillin NEXT Potassium*) or (Clavulanate NEXT Amoxicillin NEXT Combination*) or Augmentin*):ti,ab 1439

#25 [mh ^"Doxycycline"] 965

#26 (Doxycycline* or Efracea* or Periostat* or Vibramycin*):ti,ab 1462

#27 (Ertapenem* or Invanz*):ti,ab 117

#28 [mh ^Erythromycin] 947

#29 [mh ^"Erythromycin Estolate"] 70

#30 [mh ^"Erythromycin Ethylsuccinate"] 87

#31 (Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*):ti,ab 1561

#32 [mh ^Floxacillin] 78

#33 (Floxacillin* or Flucloxacillin*):ti,ab 135

#34 [mh ^Framycetin] 31

#35 Framycetin:ti,ab 22

#36 [mh ^"Fusidic Acid"] 95

#37 ("Fusidic acid" or fusidate* or Fucidin*):ti,ab 183

#38 [mh ^Gentamicins] 1049

#39 (Gentamicin* or Gentamycin* or Cidomycin*):ti,ab 1633

#40 [mh ^Imipenem] 285

#41 (Imipenem* or Primaxin*):ti,ab 502

#42 [mh ^Levamisole] 355

#43 (Levamisole or ergamisol):ti,ab 602

#44 [mh ^Levofloxacin] 533

#45 (Levofloxacin* or Evoxil* or Tavanic*):ti,ab 1055

#46 [mh ^Linezolid] 180

#47 (Linezolid* or Zyvox*):ti,ab 298

#48 Meropenem*:ti,ab 371

#49 [mh ^Metronidazole] 2103

#50 Metronidazole*:ti,ab 3341

#51 [mh Neomycin] 466

#52 (neom?cin* or "Neo-Fradin"):ti,ab 393

#53 [mh ^Mupirocin] 194

#54 (Mupirocin* or Bactroban*):ti,ab 363

#55 [mh ^Ofloxacin] 860

#56 (Ofloxacin* or Tarivid*):ti,ab 883

#57 [mh ^"Penicillin V"] 308
#58 (Phenoxymethylpenicillin* or "Penicillin V"):ti,ab 340
#59 [mh ^Piperacillin] 394
#60 (Piperacillin* or Tazobactam* or Tazocin*):ti,ab 700
#61 (Retapamulin* or Altargo* or Altabax* or Altargo*).ti,ab 4278
#62 [mh ^Teicoplanin] 166
#63 (Teicoplanin* or Targocid*):ti,ab 224
#64 Tedizolid:ti,ab 46
#65 (Tigecycline* or Tygacil*):ti,ab 99
#66 [mh ^Vancomycin] 661
#67 (Vancomycin* or Vancomicin* or Vancocin*):ti,ab 1306
#68 {or #6-#67} 27393
#69 #5 and #68 164
#70 [mh Aminoglycosides] 8075
#71 Aminoglycoside*:ti,ab 663
#72 [mh Penicillins] 5287
#73 Penicillin*:ti,ab 2101
#74 [mh "beta-Lactamases"] 83
#75 [mh "beta-Lactamase inhibitors"] 84
#76 ((beta NEAR/1 Lactamase*) or betaLactamase* or beta-Lactamase*):ti,ab 535
#77 [mh ^"beta-Lactams"] 137
#78 ("beta-Lactam" or betaLactam or "beta Lactam" or "beta-Lactams" or betaLactams or "beta Lactams"):ti,ab 539
#79 [mh Carbapenems] 497
#80 (Carbapenem*):ti,ab 370
#81 [mh Cephalosporins] 4147
#82 Cephalosporin*:ti,ab 1190
#83 [mh Fluoroquinolones] 3241
#84 Fluoroquinolone*:ti,ab 781
#85 [mh Macrolides] 7870
#86 macrolide*:ti,ab 778
#87 [mh ^Polymyxins] 106
#88 Polymyxin*:ti,ab 296
#89 [mh Quinolones] 4443
#90 Quinolone*:ti,ab 523
#91 [mh Tetracyclines] 2290
#92 Tetracycline*:ti,ab 1563
#93 {or #70-#92} 31067
#94 #5 and #93 130
#95 [mh ^Chlorhexidine] 1931

#96 (Chlorhexidine* or Unisept* or Hibiscrub* or Hydrex* or Hibi or HiBiTane*):ti,ab 3065

#97 ("Dialkylcarbamoyl chloride" or "Cutimed Sorbact"):ti,ab 6

#98 [mh ^"Glucose oxidase"] 35

#99 "Glucose oxidase":ti,ab 79

#100 [mh ^"Hydrogen Peroxide"] 541

#101 ("Hydrogen peroxide" or crystacide*):ti,ab 689

#102 [mh ^Lactoperoxidase] 27

#103 (Lactoperoxidase* or Flaminal*):ti,ab 32

#104 (Octenidine* or Octenilin*):ti,ab 58

#105 (Polihexanide* or Suprasorb* or Polyhexamethylene*):ti,ab 83

#106 [mh ^"Povidone-Iodine"] 553

#107 (Povidone-Iodine* or Betadine* or Videne* or Inadine*):ti,ab 704

#108 [mh ^"Potassium Permanganate"] 6

#109 ("Potassium permanganate" or "EN-Potab" or Permitabs):ti,ab 19

#110 [mh ^Proflavine] 14

#111 proflavine*:ti,ab 12

#112 [mh ^"Silver Sulfadiazine"] 160

#113 (Silver Sulfadiazine* or Flamazine*):ti,ab 198

#114 ("reactive oxygen" or surgihoney*):ti,ab 1164

#115 [mh ^Iodine] 493

#116 (Iodine* or Iodoflex* or Iodosorb* or Iodozyme* or Oxyzyme*):ti,ab 2835

#117 [mh ^Honey] 143

#118 [mh ^Apitherapy] 18

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

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

#121 [mh "anti-infective agents, local"] 1990

#122 (Antiseptic* or anti-septic* or anti septic* or anti-infective* or anti infective* or antiinfective* or microbicide*):ti,ab 1848

#123 [mh ^"acetic acid"] 187

#124 (vinegar* or acetic acid*):ti,ab 643

#125 [mh ^"sodium bicarbonate"] 610

#126 ((bicarbonate* or baking*) NEAR/2 (sodium* or soda*)):ti,ab 1110

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

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

#129 [mh ^"magnesium sulfate"] 817

#130 ((Magnesium* or Epsom*) NEAR/2 (sulfate* or sulphate* or salt*)):ti,ab 1667

#131 {or #95-#130} 14162

#132 #5 and #131 25

#133 [mh ^"watchful waiting"] 256

#134 "no intervention*":ti,ab 3698

#135 (watchful* NEAR/2 wait*):ti,ab 410

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

#137 (expectant* NEAR/2 manage*):ti,ab 630

#138 (active* NEAR/2 surveillance*):ti,ab 475

#139 (observing or observe or observes or observation or observations):ti,ab 48743

#140 {or #133-#139} 53780

#141 5 and 138 9613

#142 [mh ^"inappropriate prescribing"] 109

#143 ((delay* or defer*) NEAR/3 (treat* or therap* or interven*)):ti,ab 4148

#144 ((prescription* or prescrib*) NEAR/3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misuse* or "mis-us*" or overus* or "over-us*" or "over-prescri*" or abuse*)):ti,ab 3235

#145 ((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*") NEAR/3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misus* or "mis-us*" or overus* or "over-us*" or "over-prescri*" or abuse*)):ti,ab 8323

#146 {or #142-#145} 15190

#147 #5 and #146 39

#148 [mh ^"anti-infective agents"] or [mh "anti-bacterial agents"] 12874

#149 (antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*"):ti,ab 24588

#150 {or #148-#149} 30793

#151 #5 and #150 150

#152 #69 or #94 or #132 or #147 or #151 245

#153 #152 with Cochrane Library publication date Between Jan 2000 and Dec 2018, in Cochrane Reviews 4

#154 #69 or #94 or #132 or #147 224

#155 #154 with Publication Year from 2000 to 2018, in Trials 115

#156 "clinicaltrials.gov".so 171368

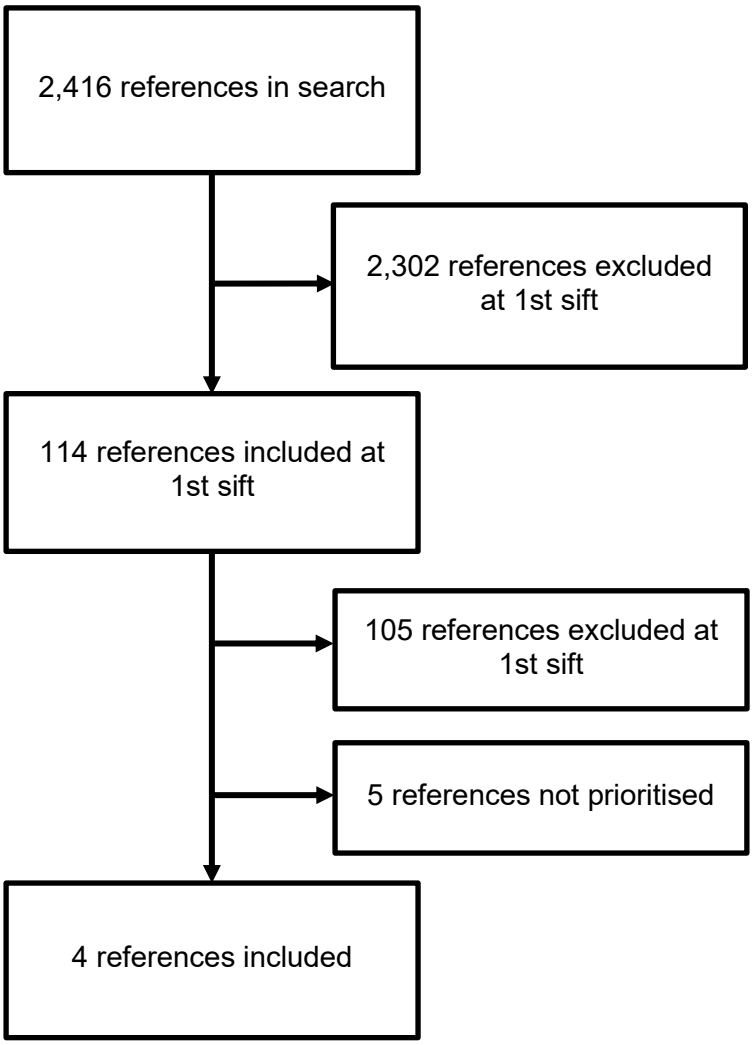
#157 #155 not #156 80

DARE / HTA

1	MeSH DESCRIPTOR impetigo	2
2	MeSH DESCRIPTOR soft tissue infections	25
3	MeSH DESCRIPTOR pyoderma	0
4	(impetigo*)	5
5	#1 OR #2 OR #3 OR #4	29

Only doing condition searches - this gives 16 from DARE and 1 from HTA, all 2000 onwards.

Appendix D: Study flow diagram



Appendix E: Evidence prioritisation

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
Efficacy of antibiotics						
Topical antibiotic						
Koning et al. 2012	Systematic review	Mupirocin	Placebo	Cure or improvement	Prioritised	Most comprehensive analysis available, including largest total sample size and meta-analysis.
		Fusidic acid	Placebo			
Edge et al. 2017	Systematic review of systematic reviews	Mupirocin	Placebo	Cure or improvement	Not prioritised	This is a less comprehensive analysis, does not include meta-analysis, and does not include additional data to that in the prioritised systematic review.
		Fusidic acid	Placebo			
Hebert et al. 2018	Pooled analysis of RCTs	Ozenoxacin	Placebo	Clinical and microbiological success	Prioritised	Details an intervention not included in Koning et al. 2012.
Oral antibiotic						
Koning et al. 2012	Systematic review	Phenoxymethyl-penicillin	Placebo	Cure or improvement	Prioritised	Most comprehensive analysis available, including largest total sample size and meta-analysis.
Antibiotics compared with other treatment						
Topical antibiotic compared with antiseptic						
Koning et al. 2012	Systematic review	Fusidic acid	Hydrogen peroxide	Cure or improvement	Prioritised	Highest quality systematic review identified for this comparison (most comprehensive data and analysis available).
Topical antibiotic compared with topical steroid						

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
Koning et al. 2012	Systematic review	Gentamicin	Betamethasone valerate	Cure or improvement	Prioritised	Highest quality systematic review identified for this comparison (most comprehensive data and analysis available).
Topical antibiotic plus topical steroid compared with topical steroid						
Koning et al. 2012	Systematic review	Gentamicin plus betamethasone valerate	Betamethasone valerate	Cure or improvement	Prioritised	Highest quality systematic review identified for this comparison (most comprehensive data and analysis available).
Topical antibiotic compared with antifungal						
Koning et al. 2012	Systematic review	Mupirocin	Terbinafine	Cure or improvement	Prioritised	Highest quality systematic review identified for this comparison (most comprehensive data and analysis available).
Choice of antibiotics						
Topical antibiotic						
Koning et al. 2012	Systematic review	Mupirocin	Fusidic acid	Cure or improvement	Prioritised	Highest quality systematic review identified for this comparison (most comprehensive data and analysis available).
		Mupirocin	Neomycin			
		Mupirocin	Polymyxin B/neomycin			
		Fusidic acid	Neomycin/bacitracin			
		Gentamicin	Neomycin			
Oral antibiotic						
Koning et al. 2012	Systematic review	Macrolides	Penicillins	Cure or improvement	Prioritised	Highest quality systematic review identified for this comparison (most comprehensive analysis
		Erythromycin	Phenoxymethylpenicillin			
		Erythromycin	Amoxicillin			
		Azithromycin	Erythromycin			

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
		Co-amoxiclav	Amoxicillin			including largest total sample size and meta-analysis).
		Cefalexin	Cefadroxil			
		Cefalexin	Phenoxymethylpenicillin			
		Cefalexin	Erythromycin			
		Cefalexin	Azithromycin			
		Cefaclor	Azithromycin			
		Cefaclor	Co-amoxiclav			
		Cefadroxil	Flucloxacillin			
Bucko et al. 2002	RCT	Cefditoren	Cefuroxime	Cure	Not prioritised	Intervention not available in the UK. Not prioritised because there is evidence available for oral antibiotics that are licensed in the UK.
		Cefditoren	Cefadroxil			
Tarshis et al. 2001	RCT	Gatifloxacin	Levofloxacin	Cure	Not prioritised	Intervention not available in the UK. Not prioritised because there is evidence available for oral antibiotics that are licensed in the UK.
Dual antibiotic						
Koning et al. 2012	Systematic review	Cefdinir plus tetracycline	Tetracycline	Cure or improvement	Prioritised	Highest quality systematic review identified for this comparison (most comprehensive data and analysis available).
		Minomycin plus tetracycline	Tetracycline			
		Fosfomycin plus tetracycline	Tetracycline			
Antibiotic course length						
Shorter course antibiotic compared with longer course antibiotic						
Bowen et al. 2014	RCT	3 day course co-trimoxazole	5 day course co-trimoxazole	Treatment success	Prioritised	Highest quality evidence identified for this comparison.

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
						(most comprehensive data available).
Antibiotic route of administration						
Topical antibiotic compared with oral antibiotic						
Koning et al. 2012	Systematic review	Mupirocin	Erythromycin	Cure or improvement	Prioritised	Highest quality systematic review identified for this comparison (most comprehensive analysis, including largest total sample size and meta-analysis).
		Mupirocin	Cefalexin			
		Mupirocin	Ampicillin			
		Fusidic acid	Erythromycin			
		Chloramphenicol	Erythromycin			
Edge et al. 2017	Systematic review of systematic reviews	Mupirocin	Erythromycin	Cure or improvement	Not prioritised	A higher quality systematic review has been prioritised for this comparison (a more comprehensive analysis, including a larger total sample size and meta-analysis).
		Mupirocin	Cefalexin			
		Mupirocin	Ampicillin			
Intramuscular antibiotic compared with oral antibiotic						
Al-Samman et al. 2014	RCT	Ceftriaxone	Cefadroxil	Cure and recurrence	Prioritised	Highest quality evidence identified for this comparison (most comprehensive data available)
Bowen et al. 2014	RCT	Benzathine penicillin	Co-trimoxazole	Treatment success	Prioritised	Highest quality evidence identified for this comparison (most comprehensive data available).
Bowen et al. 2017	Systematic review	Benzathine penicillin	Co-trimoxazole	Treatment success	Not prioritised	A higher quality RCT including more data and outcome reporting has been prioritised over this systematic review (Bowen et al. 2017 includes very limited data from 2 relevant RCTs [Bowen. et al. 2014 which

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
						is prioritised and a pilot RCT including 13 participants]).
Antibiotic concentration						
Chamny et al. 2016	RCT	Minocycline 1%	Minocycline 4%	Clinical success	Not prioritised	Intervention not available in the UK, therefore evidence on concentration not applicable to UK practice
Abbreviations: RCT – randomised control trial						

[1] See appendix F for full references of included studies
[2] See appendix I for full references of not-prioritised studies, with detailed reasons for not prioritising these studies

Appendix F: Included studies

Al-Samman D K (2014) Comparison of single-dose ceftriaxone versus seven days cefadroxil in addition to fucidic acid cream as adjuvant therapy for the treatment of children with impetigo. Pharmacie Globale 5(1)

Bowen A C, Tong S Y. C, Andrews R M, O'Meara I M, McDonald M I, Chatfield M D, Currie B J, and Carapetis J R (2014) Short-course oral co-trimoxazole versus intramuscular benzathine benzylpenicillin for impetigo in a highly endemic region: An open-label, randomised, controlled, non-inferiority trial. The Lancet 384(9960), 2132-2140

Hebert Adelaide A, Albareda Nuria, Rosen Theodore, Torrelo Antonio, Grimalt Ramon, Rosenberg Noah, Zsolt Ilonka, and Masramon Xavier (2018) Topical Antibacterial Agent for Treatment of Adult and Pediatric Patients with Impetigo: Pooled Analysis of Phase 3 Clinical Trials. Journal of drugs in dermatology: JDD 17(10), 1051-1057

Koning Sander, van der Sande, Renske, Verhagen Arianne P, van Suijlekom-Smit, Lisette W A, Morris Andrew D, Butler Christopher C, Berger Marjolein, van der Wouden, and Johannes C (2012) Interventions for impetigo. The Cochrane database of systematic reviews 1, CD003261

Appendix G: Quality assessment of included studies

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

Study reference	Koning et al. 2012
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes
What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

Table 3: Overall risk of bias/quality assessment – RCTs (RCT checklist)

Study reference	Al-Samman et al. 2014	Bowen et al. 2014	Hebert et al. 2018
Did the trial address a clearly focused issue?	Yes	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes	Yes
Were patients, health workers and study personnel blinded?	No[a]	Yes[b]	Yes
Were the groups similar at the start of the trial?	Yes	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes	Yes
How large was the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes	No[c]	Yes

Study reference	Al-Samman et al. 2014	Bowen et al. 2014	Hebert et al. 2018
Were all clinically important outcomes considered?	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles

[a] Participants could not be blinded due to nature of the study; however, also no description of outcome assessor blinding
[b] Not possible to blind participants, but outcome assessors were blinded
[c] Study conducted in an Indigenous Australian population which may not be applicable to UK practice

Appendix H: GRADE profiles

H.1 Efficacy of antibiotics

H.1.1 Topical antibiotics

Table 4: GRADE profile – topical antibiotics compared with placebo

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Placebo	Relative (95% CI)	Absolute		
Topical antibiotics[1] - cure or improvement – overall analysis												
6[2]	randomised trials	serious[3]	serious[4]	serious[5,6]	no serious imprecision	none	220/312 (70.5%)	77/263 (29.3%)	RR 2.24 (1.61 to 3.13)	363 more per 1000 (from 179 more to 624 more)	⊕OOO VERY LOW	CRITICAL
Fusidic acid[7] - cure or improvement												
1[2]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	42/76 (55.3%)	10/80 (12.5%)	RR 4.42 (2.39 to 8.17)	428 more per 1000 (from 174 more to 896 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mupirocin[8] - cure or improvement												
3[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness[5]	no serious imprecision	none	58/81 (71.6%)	30/92 (32.6%)	RR 2.18 (1.58 to 3.00)	385 more per 1000 (from 189 more to 652 more)	⊕⊕⊕O MODERATE	CRITICAL
Mupirocin[7] - nausea or vomiting												
1[2]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[10]	none	0/52 (0%)	1/52 (1.9%)	RR 3.00 (0.13 to 71.99) Peto OR 0.14 (0.00 to 6.82)	38 more per 1000 (from 17 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Ozenoxacin[11] - clinical success (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	169/357 (47.3%)	111/354 (31.4%)	RR 1.51 (1.25 to 1.82)	160 more per 1000 (from 78 more to 257 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Ozenoxacin[11] - clinical failure (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[13]	none	188/357 (52.7%)	243/354 (68.6%)	RR 0.77 (0.68 to 0.87)	158 fewer per 1000 (from 89 fewer to 220 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Ozenoxacin[11] - microbiological success (day 3 to 4)												

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Placebo	Relative (95% CI)	Absolute		
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	218/279 (78.1%)	134/271 (49.4%)	RR 1.58 (1.38 to 1.81)	287 more per 1000 (from 188 more to 401 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Ozenoxacin[11] - microbiological failure (day 3 to 4)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	53/271 (19.6%)	122/256 (47.7%)	RR 0.41 (0.31 to 0.54)	281 fewer per 1000 (from 219 fewer to 329 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Ozenoxacin[11] - microbiological success (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[14]	none	237/261 (90.8%)	173/248 (69.8%)	RR 1.30 (1.19 to 1.43)	209 more per 1000 (from 133 more to 300 more)	⊕⊕⊕O MODERATE	CRITICAL
Ozenoxacin[11] - microbiological failure (day 6 to 7)												
1[12]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	24/261 (9.2%)	75/248 (30.2%)	RR 0.30 (0.20 to 0.47)	212 fewer per 1000 (from 160 fewer to 242 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Abbreviations: CI – confidence interval; RR – relative risk; NA – not applicable; OR – odds ratio

[1] Topical antibiotics include: mupirocin - 2% 3 times a day for 7 to 9 days; 2% once daily until cleared or 2% 3 times daily for 10 to 12 days; fusidic acid - 2% 3 times a day; topical retapamulin - 1% 2 times daily for 5 days; bacitracin ointment, 2 times daily (unreported dose or course length)
[2] Koning et al. 2012
[3] Downgraded 1 level - 1 or more studies included were deemed at high risk of bias in 1 or more domains by systematic review authors
[4] Downgraded 1 level - heterogeneity >50%
[5] Not downgraded - 1 study includes a range of skin infections, with a subgroup for impetigo described separately and reported here
[6] Downgraded 1 level - not all topical antibiotics are available in UK
[7] Fusidic acid - 2% 3 times a day
[8] Mupirocin - 2% 3 times a day for 7 to 9 days; 2% once daily until cleared or 2% 3 times daily for 10 to 12 days
[9] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[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] Ozenoxacin 1% cream - participants instructed to apply thin layer (a fingertip unit, approximately 0.5 g) to the affected areas twice daily
[12] Hebert et al. 2018; pooled-analysis of 2 randomised controlled trials (Rosen et al. 2018 and Gropper et al. 2014)
[13] 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
[14] 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 ozenoxacin

H.1.2 Oral antibiotics

Table 5: GRADE profile – oral phenoxymethylpenicillin compared with placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral antibiotics[1]	Placebo	Relative (95% CI)	Absolute		
Cure or improvement												
1[2]	randomised trials	serious[3]	NA	no serious indirectness	very serious[4]	none	3/18 (16.7%)	0/20 (0%)	RR 7.74 (0.43 to 140.26) Peto OR 9.32 (0.91 to 95.77)	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Oral phenoxymethylpenicillin – 40 to 60,000 units/kg/day in 3 doses
[2] Koning et al. 2012
[3] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[4] 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

H.2 Antibiotics compared with other treatment

H.2.1 Topical antibiotic compared with antiseptic

Table 6: GRADE profile – topical fusidic acid compared with hydrogen peroxide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fusidic acid[1]	Hydrogen peroxide[2]	Relative (95% CI)	Absolute		
Cure or improvement												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	Serious[4]	none	105/128 (82.0%)	92/128 (71.9%)	RR 1.14 (1.00 to 1.31)	101 more per 1000 (from 0 more to 223 more)	⊕⊕⊕O MODERATE	CRITICAL
Fusidic acid[1] vs hydrogen peroxide[2] - adverse events leading to withdrawal												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	3/128 (2.3%)	0/128 (0%)	RR 7.00 (0.37 to 134.16) Peto OR 7.51 (0.77 to 72.81)	-	⊕⊕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[1]	Hydrogen peroxide[2]	Relative (95% CI)	Absolute		
Fusidic acid[1] vs hydrogen peroxide[2] - mild side effects												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	9/128 (7.0%)	13/128 (10.2%)	RR 0.69 (0.31 to 1.56)	31 fewer per 1000 (from 70 fewer to 57 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk; NA – not applicable; OR – odds ratio												

[1] Fusidic acid cream 2% 2 to 3 times daily for up to 21 days
[2] Hydrogen peroxide cream, 1% 2 to 3 times daily for up to 21 days
[3] Koning et al. 2012
[4] 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
[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

H.2.2 Topical antibiotic compared with topical steroid

Table 7: GRADE profile – topical gentamicin compared with topical betamethasone valerate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic[1]	Topical steroid[2]	Relative (95% CI)	Absolute		
Cure/improvement[3]												
1[4]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[5]	none	8/27 (29.6%)	15/27 (55.6%)	RR 0.53 (0.27 to 1.04)	261 fewer per 1000 (from 406 fewer to 22 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Topical antibiotic: gentamicin cream 3 times daily
[2] Topical steroid: betamethasone valerate cream 3 times daily
[3] Population: secondary impetigo
[4] Koning et al. 2012
[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 betamethasone

H.2.3 Topical antibiotic plus topical steroid compared with topical steroid

Table 8: GRADE profile – topical gentamicin plus topical betamethasone valerate compared with topical betamethasone valerate

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		
Cure or improvement (secondary impetigo)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	18/25 (72.0%)	15/27 (55.6%)	RR 1.30 (0.85 to 1.97)	167 more per 1000 (from 83 fewer to 539 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Topical antibiotic plus topical steroid: gentamicin cream 3 times daily plus betamethasone valerate cream 3 times daily
[2] Topical steroid: betamethasone valerate cream 3 times daily
[3] Koning et al. 2012
[4] 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 steroid plus antibiotic

H.2.4Topical antibiotic compared with antifungal

Table 9: GRADE profile – topical mupirocin compared with topical terbinafine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic[1]	Topical antifungal[2]	Relative (95% CI)	Absolute		
Cure												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	25/31 (80.6%)	18/31 (58.1%)	RR 1.39 (0.98 to 1.96)	226 more per 1000 (from 12 fewer to 557 more)	⊕⊕OO LOW	CRITICAL
Adverse events (burning, stinging, itching or rash)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[6]	none	1/31 (3.2%)	2/31 (6.5%)	RR 0.50 (0.05 to 5.23)	32 fewer per 1000 (from 61 fewer to 273 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Topical antibiotic - mupirocin 2% 3 times daily for 10 days
[2] Topical antifungal - terbinafine 1% 3 times daily for 10 days
[3] Koning et al. 2012
[4] Downgraded1 level - study deemed to be at high risk of bias in 1 or more domains by systematic review authors
[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

H.3 Choice of antibiotics

H.3.1Topical antibiotics

Table 10: GRADE profile – topical mupirocin compared with topical fusidic acid

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical mupirocin[1]	Topical fusidic acid[2]	Relative (95% CI)	Absolute		
Cure or improvement												
4[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness[5]	no serious imprecision	none	199/236 (84.3%)	174/204 (85.3%)	RR 1.03 (0.95 to 1.11)	26 more per 1000 (from 43 fewer to 94 more)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of skin reactions												
3[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	no serious imprecision	none	22/523 (4.2%)	6/422 (1.4%)	RR 3.25 (1.37 to 7.70)[7]	32 more per 1000 (from 5 more to 95 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk												

[1] Topical mupirocin – 2% 2 to 3 times daily for 6 to 8 days
[2] Topical fusidic acid – 2% 3 times daily for up to 8 days
[3] Koning et al. 2012
[4] Downgraded 1 level - 1 or more studies deemed at high risk of bias in 1 or more domains by systematic review authors
[5] Not downgraded - study includes a range of skin infections, with a subgroup for impetigo described separately and reported here
[6] Downgraded 1 level - includes participants with a range of bacterial skin infections, not only impetigo
[7] NICE analysis - meta-analysis not presented by systematic review and calculated by NICE

Table 11: GRADE profile – topical mupirocin compared with topical neomycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical mupirocin[1]	Topical neomycin[2]	Relative (95% CI)	Absolute		
Cure or improvement												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[5]	none	15/15 (100%)	13/17 (76.5%)	RR 1.29 (0.98 to 1.71)	222 more per 1000 (from 15 fewer to 543 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Topical mupirocin - 2% 2 times daily for 10 to 11 days
[2] Topical neomycin – 1% 2 times daily for 10 to 11 days
[3] Koning et al. 2012
[4] Downgraded 1 level - topical neomycin is classed as a product that is less than suitable for prescribing

[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 mupirocin

Table 12: GRADE profile – topical mupirocin compared with topical polymyxin B/neomycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical mupirocin[1]	Topical polymyxin B/neomycin[2]	Relative (95% CI)	Absolute		
Cure or improvement												
1[3]	randomised trials	no serious risk of bias	NA	serious[4,5]	very serious[6]	none	2/2 (100%)	5/6 (83.3%)	RR 1.06 (0.56 to 2.01)	50 more per 1000 (from 367 fewer to 842 more)	⊕OOO VERY LOW	CRITICAL
Incidence of rash												
1[3]	randomised trials	no serious risk of bias	NA	very serious[5,7]	very serious[6]	none	0/24 (0%)	1/26 (3.8%)	RR 0.35 (0.01 to 8.93) Peto OR 0.15 (0.00 to 7.39)	25 fewer per 1000 (from 38 fewer to 305 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk; OR – odds ratio												

[1] Topical mupirocin – 2% 3 times daily for 7 days
[2] Topical polymyxin B/neomycin – 3 times daily for 7 days
[3] Koning et al. 2012
[4] Not downgraded - study includes a range of skin infections, with a subgroup for impetigo described separately and reported here
[5] Downgraded 1 level - topical neomycin is classed as a product that is less than suitable for prescribing
[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 - includes participants with a range of bacterial skin infections, not only impetigo

Table 13: GRADE profile – topical fusidic acid compared with topical neomycin/bacitracin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical fusidic acid[1]	Topical neomycin/ bacitracin[2]	Relative (95% CI)	Absolute		
Cure or improvement (bullous impetigo)												
1[3]	randomised trials	serious[4]	NA	serious[5]	serious[6]	none	10/12 (83.3%)	1/12 (8.3%)	RR 10.0 (1.51 to 66.43)	750 more per 1000 (from 42 more to 1000 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Topical fusidic acid – 2% 3 times daily for 10 days
[2] Topical neomycin/bacitracin ointment – 3 times daily for 10 days

[3] Koning et al. 2012
[4] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[5] Downgraded 1 level - topical neomycin is classed as a product that is less than suitable for prescribing
[6] Downgraded 1 level - very wide confidence intervals

Table 14: GRADE profile – topical gentamicin compared with topical neomycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical gentamicin[1]	Topical neomycin[2]	Relative (95% CI)	Absolute		
Cure or improvement												
1[3]	randomised trials	serious[4]	NA	serious[5]	serious[6]	none	60/84 (71.4%)	22/44 (50.0%)	RR 1.43 (1.03 to 1.98)	215 more per 1000 (from 15 more to 490 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Topical gentamicin – 1% 3 times daily, unreported duration
[2] Topical neomycin ointment – 0.5% 3 times daily, unreported duration
[3] Koning et al. 2012
[4] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[5] Downgraded 1 level - topical neomycin is classed as a product that is less than suitable for prescribing
[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 benefit with gentamicin

H.3.2Oral antibiotics

Table 15: GRADE profile – oral macrolides compared with oral penicillins

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral macrolide[1]	Oral penicillin[2]	Relative (95% CI)	Absolute		
Cure or improvement – overall analysis												
7[3]	randomised trials	serious[4]	no serious inconsistency	serious[5,6]	no serious imprecision	none	172/193 (89.1%)	145/170 (85.3%)	RR 1.06 (0.98 to 1.15)	51 more per 1000 (from 17 fewer to 128 more)	⊕⊕OO LOW	CRITICAL
Erythromycin[1] vs phenoxymethylpenicillin[2] – cure or improvement												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[7]	none	38/39 (97.4%)	30/40 (75.0%)	RR 1.29 (1.07 to 1.56)	217 more per 1000 (from 53 more to 420 more)	⊕⊕OO LOW	CRITICAL
Erythromycin[1] vs amoxicillin[2] – cure or improvement												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral macrolide[1]	Oral penicillin[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[8]	NA	no serious indirectness	no serious imprecision	none	58/65 (89.2%)	57/64 (89.1%)	RR 1.00 (0.89 to 1.13)	0 fewer per 1000 (from 98 fewer to 116 more)	⊕⊕⊕O MODERATE	CRITICAL
Erythromycin[1] vs amoxicillin[2] - diarrhoea												
1[3]	randomised trials	serious[8]	NA	no serious indirectness	serious[9]	none	11/65 (16.9%)	2/64 (3.1%)	RR 5.42 (1.25 to 23.47)	138 more per 1000 (from 8 more to 702 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Macrolides include: erythromycin - 30 to 40 mg/kg/day in 3 to 4 daily doses for 10 days; azithromycin - 250mg twice daily (day 1), once daily (day 2 to 5) for 5 days or 10 mg/kg/day (max. 500mg) once daily for 3 days; clindamycin - 150 mg 4 times daily or 300 mg twice daily
[2] Penicillins include: phenoxymethylpenicillin - 40 to 50 mg/kg/day in 3 to 4 daily doses for 10 days; dicloxacillin - 25 mg/kg/day in 4 daily doses for 10 days; amoxicillin - 50 mg/kg/day for 7 days; cloxacillin - 500 mg 4 times daily for 7 days; dicloxacillin/flucloxacillin - 12.5 to 25 mg/kg/day and 500 to 3000 mg/day in 4 doses for 7 days; dicloxacillin -250 mg 4 times daily
[3] Koning et al. 2012
[4] Downgraded 1 level - 1 or more studies deemed at high risk of bias in 1 or more domains by systematic review authors
[5] Not downgraded - 1 or more studies includes a range of skin infections, with a subgroup for impetigo described separately and reported here
[6] Downgraded 1 level - not all antibiotics included in comparison are available in UK
[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 macrolide
[8] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[9] Downgraded 1 level - very wide confidence intervals

Table 16: GRADE profile – oral azithromycin compared with oral erythromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral azithromycin[1]	Oral erythromycin[2]	Relative (95% CI)	Absolute		
Cure or improvement												
1[3]	randomised trials	serious[4]	NA	no serious indirectness[5]	serious[6]	none	28/35 (80.0%)	21/31 (67.7%)	RR 1.18 (0.88 to 1.58)	122 more per 1000 (from 81 fewer to 393 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Azithromycin - 250 mg twice daily (day 1) and once daily (day 2 to 5) for 5 days
[2] Erythromycin - 500 mg 4 times daily for 7 days
[3] Koning et al. 2012
[4] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[5] Not downgraded - study includes a range of skin infections, with a subgroup for impetigo described separately and reported here

[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 benefit with azithromycin

Table 17: GRADE profile – oral co-amoxiclav compared with oral amoxicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral co-amoxiclav[1]	Oral amoxicillin[2]	Relative (95% CI)	Absolute		
Cure or improvement												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	21/22 (95.5%)	15/22 (68.2%)	RR 1.40 (1.04 to 1.89)	273 more per 1000 (from 27 more to 607 more)	⊕⊕OO LOW	CRITICAL
Vomiting or diarrhoea												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[6]	none	0/22 (0%)	2/22 (9.1%)	RR 0.20 (0.01 to 3.94) Peto OR 0.13 (0.01 to 2.13)	73 fewer per 1000 (from 90 fewer to 267 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Co-amoxiclav syrup - 40/10 mg/kg/day in 3 daily doses for 10 days
[2] Amoxicillin syrup - 40 mg/kg/day in 3 daily doses for 10 days
[3] Koning et al. 2012
[4] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[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 co-amoxiclav
[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

Table 18: GRADE profile – oral cefalexin compared with oral cefadroxil

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cefalexin[1]	Oral cefadroxil[2]	Relative (95% CI)	Absolute		
Cure or improvement												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	41/45 (91.1%)	47/51 (92.2%)	RR 0.99 (0.88 to 1.12)	9 fewer per 1000 (from 111 fewer to 111 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Cephalexin – 30 mg/kg/day (max 1g) in 2 daily doses for 10 days
[2] Cefadroxil - 30 mg/kg/day (max 1 g) in 1 daily dose for 10 days
[3] Koning et al. 2012
[4] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors

Table 19: GRADE profile – oral cefalexin compared with oral phenoxymethylpenicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cefalexin[1]	Oral phenoxy-methylpenicillin[2]	Relative (95% CI)	Absolute		
Cure or improvement												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	23/23 (100%)	19/25 (76.0%)	RR 1.31 (1.04 to 1.64)	236 more per 1000 (from 30 more to 486 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Oral cefalexin – 40 to 50 mg/kg/day in 3 daily doses for 10 days
[2] Oral phenoxymethylpenicillin - 40 to 50 mg/kg/day in 3 daily doses for 10 days
[3] Koning et al. 2012
[4] 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 cephalexin

Table 20: GRADE profile – oral cefalexin compared with oral erythromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cefalexin[1]	Oral erythromycin[2]	Relative (95% CI)	Absolute		
Cure or improvement												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	23/23 (100%)	24/25 (96.0%)	RR 1.04 (0.93 to 1.16)	38 more per 1000 (from 67 fewer to 154 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Oral cefalexin – 40 to 50 mg/kg/day in 3 daily doses for 10 days
[2] Oral erythromycin – 30 to 50 mg/kg/day in 3 daily doses for 10 days
[3] Koning et al. 2012

Table 21: GRADE profile – oral cefalexin compared with oral azithromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cefalexin[1]	Oral azithromycin[2]	Relative (95% CI)	Absolute		
Cure or improvement												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cefalexin[1]	Oral azithromycin[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[4]	NA	no serious indirectness[5]	very serious[6]	none	6/8 (75.0%)	5/10 (50.0%)	RR 1.50 (0.72 to 3.14)	250 more per 1000 (from 140 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Gastrointestinal adverse events												
1[3]	randomised trials	serious[4]	NA	serious[7]	very serious[6]	none	30/182 (16.5%)	20/184 (10.9%)	RR 1.62 (0.88 to 2.97)	67 more per 1000 (from 13 fewer to 214 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Oral cefalexin – 500 mg twice daily for 10 days
[2] Oral azithromycin – 500 mg on day 1, 250 mg for day 2 to 5, for 5 days total
[3] Koning et al. 2012
[4] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[5] Not downgraded - study includes a range of skin infections, with a subgroup for impetigo described separately and reported here
[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 - includes participants with bacterial skin infections other than impetigo

Table 22: GRADE profile – oral cefaclor compared with oral azithromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cefaclor[1]	Oral azithromycin[2]	Relative (95% CI)	Absolute		
Cure or improvement												
1[3]	randomised trials	serious[4]	NA	no serious indirectness[5]	no serious imprecision	none	49/51 (96.1%)	41/44 (93.2%)	RR 1.03 (0.94 to 1.14)	28 more per 1000 (from 56 fewer to 130 more)	⊕⊕⊕O MODERATE	CRITICAL
Mild skin side effects												
1[3]	randomised trials	serious[4]	NA	serious[6]	very serious[7]	none	2/100 (2.0%)	3/100 (3.0%)	RR 0.67 (0.11 to 3.90)	10 fewer per 1000 (from 27 fewer to 87 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Oral cefaclor – 20 mg/kg/day once daily for 10 days
[2] Oral azithromycin – 10 mg/kg/day once daily for 3 days
[3] Koning et al. 2012
[4] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[5] Not downgraded - study includes a range of skin infections, with a subgroup for impetigo described separately and reported here
[6] Downgraded 1 level - includes participants with bacterial skin infections other than impetigo

[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

Table 23: GRADE profile – oral cefaclor compared with oral co-amoxiclav

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cefaclor[1]	Oral co-amoxiclav[2]	Relative (95% CI)	Absolute		
Cure or improvement												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness[4]	serious[5]	none	13/16 (81.3%)	16/18 (88.9%)	RR 0.91 (0.69 to 1.22)	80 fewer per 1000 (from 276 fewer to 196 more)	⊕⊕⊕O MODERATE	CRITICAL
Mild diarrhoea												
1[3]	randomised trials	no serious risk of bias	NA	serious[6]	serious[7]	none	20/184 (10.9%)	30/182 (16.5%)	RR 0.66 (0.39 to 1.12)	56 fewer per 1000 (from 101 fewer to 20 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Oral cefaclor – 20 mg/kg/day in 3 daily doses
[2] Oral co-amoxiclav – 125/30, dose equivalent to 20 mg amoxicillin/kg/day in 3 daily doses for 10 days
[3] Koning et al. 2012
[4] Not downgraded - study includes a range of skin infections, with a subgroup for impetigo described separately and reported here
[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 co-amoxiclav
[6] Downgraded 1 level - includes participants with bacterial skin infections other than impetigo
[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 co-amoxiclav

Table 24: GRADE profile – oral cefadroxil compared with oral flucloxacillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cefadroxil[1]	Oral flucloxacillin[2]	Relative (95% CI)	Absolute		
Cure or improvement												
1[3]	randomised trials	serious[4]	NA	no serious indirectness[5]	serious[6]	none	25/33 (75.8%)	25/27 (92.6%)	RR 0.82 (0.66 to 1.02)	167 fewer per 1000 (from 315 fewer to 19 more)	⊕⊕OO LOW	CRITICAL
Severe adverse events (stomach ache/rash/fever/vomiting)												
1[3]	randomised trials	serious[4]	NA	serious[7]	very serious[8]	none	14/327 (4.3%)	2/234 (0.85%)	RR 5.01 (1.15 to 21.83)	34 more per 1000 (from 1 more to 178 more)	⊕OOO VERY LOW	CRITICAL
Diarrhoea												
1[3]	randomised trials	serious[4]	NA	serious[7]	no serious imprecision	none	14/327 (4.3%)	87/324 (26.9%)	RR 0.16 (0.09 to 0.27)	226 fewer per 1000 (from 196 fewer to 244 fewer)	⊕⊕OO 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]	Oral flucloxacillin[2]	Relative (95% CI)	Absolute		
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Oral cefadroxil – 40 mg/kg/day for 10 days
[2] Oral flucloxacillin – tablets 750 mg twice daily or suspension 30 to 50 mg/kg/day in 2 to 3 daily doses for 10 days
[3] Koning et al. 2012
[4] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[5] Not downgraded - study includes a range of skin infections, with a subgroup for impetigo described separately and reported here
[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 benefit with flucloxacillin
[7] Downgraded 1 level - includes participants with bacterial skin infections other than impetigo
[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 or appreciable harm with cefadroxil; very wide confidence intervals

H.3.3 Dual antibiotics

Table 25: GRADE profile – oral antibiotic plus topical antibiotic compared with topical antibiotic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral antibiotic plus topical antibiotic[1]	Topical antibiotic[2]	Relative (95% CI)	Absolute		
Cefdinir plus tetracycline versus tetracycline - cure												
1[3]	randomised trials	serious[4]	NA	serious[5]	very serious[6]	none	3/6 (50.0%)	22/28 (78.6%)	RR 0.64 (0.28 to 1.45)	285 fewer per 1000 (from 566 fewer to 354 more)	⊕OOO VERY LOW	CRITICAL
Minomycin plus tetracycline versus tetracycline - cure												
1[3]	randomised trials	serious[4]	NA	serious[5]	serious[7]	none	5/5 (100%)	22/28 (78.6%)	RR 1.18 (0.87 to 1.61)	141 more per 1000 (from 102 fewer to 479 more)	⊕OOO VERY LOW	CRITICAL
Fosfomycin plus tetracycline versus tetracycline - cure												
1[3]	randomised trials	serious[4]	NA	serious[5]	very serious[6]	none	6/10 (60.0%)	22/28 (78.6%)	RR 0.76 (0.44 to 1.31)	189 fewer per 1000 (from 440 fewer to 244 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Oral antibiotic plus topical antibiotic - oral cefdinir 9 mg/kg/day for 7 days, oral minomycin 4 mg/kg/day for 7 days or oral fosfomycin 40 mg/kg/day for 7 days, plus topical tetracycline 3% 3 times daily
[2] Topical antibiotic monotherapy - tetracycline 3% 3 times daily for 7 days
[3] Koning et al. 2012
[4] Downgraded 1 level - study deemed at high risk of bias in 1 or more domains by systematic review authors
[5] Downgraded 1 level - all or most of antibiotics included in comparison are not available in UK
[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 benefit with tetracycline plus minomycin

H.4 Antibiotic course length

H.4.1 Shorter course antibiotics compared with longer course antibiotics

Table 26: GRADE profile – 3 day course compared with 5 day course of oral co-trimoxazole

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-trimoxazole 3 day course[1]	Co-trimoxazole 5 day course[2]	Relative (95% CI)	Absolute		
Treatment success intention to treat (day 7)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision[5]	none	147/173 (85.0%)	136/161 (84.5%)	RR 1.01 (0.92 to 1.10)[6]	8 more per 1000 (from 68 fewer to 84 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment success per protocol (day 7)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision[5]	none	135/159 (84.9%)	129/151 (85.4%)	RR 0.99 (0.91 to 1.09)[6]	9 fewer per 1000 (from 77 fewer to 77 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical success (day 7)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision[5]	none	171/173 (98.8%)	161/161 (100%)	RR 0.99 (0.97 to 1.01)[6]	10 fewer per 1000 (from 30 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
Resolution of sores from whole body (day 7)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-trimoxazole 3 day course[1]	Co-trimoxazole 5 day course[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision[5]	none	152/173 (87.9%)	144/160 (90.0%)	RR 0.98 (0.91 to 1.05)[6]	18 fewer per 1000 (from 81 fewer to 45 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment success (day 2)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision[5]	none	84/169 (49.7%)	82/166 (49.4%)	RR 1.01 (0.81 to 1.25)[6]	5 more per 1000 (from 94 fewer to 123 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical success (day 2)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision[5]	none	119/169 (70.4%)	114/166 (68.7%)	RR 1.03 (0.89 to 1.18)[6]	21 more per 1000 (from 76 fewer to 124 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] 3 day course - oral co-trimoxazole 4 mg/kg plus 20 mg/kg (maximum 160 mg plus 800 mg) twice daily
[2] 5 day course - oral co-trimoxazole 8 mg/kg plus 40 mg/kg (maximum 320 mg plus 1600 mg) once daily
[3] Bowen et al. 2014
[4] Downgraded 1 level - study conducted in an aboriginal community, where impetigo prevalence rate is higher than prevalence measured in the UK, therefore response to antibiotic treatment may be different in the local population
[5] Imprecision judged using minimal important difference of 25% relative risk increase (RRI)/reduction (RRR) as absolute difference not reported and non-inferiority margin not applicable to this comparison

[6] NICE analysis - RR calculated from raw data

H.5 Antibiotic route of administration

H.5.1 Topical antibiotic compared with oral antibiotic

Table 27: GRADE profile – topical antibiotic compared with oral antibiotic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Oral antibiotic	Relative (95% CI)	Absolute		
Mupirocin[1] versus erythromycin[2] - cure or improvement												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Oral antibiotic	Relative (95% CI)	Absolute		
10[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness[5]	no serious imprecision	none	270/298 (90.6%)	242/283 (85.5%)	RR 1.06 (1.00 to 1.13) [NICE analysis]	60 more per 1000 (from 9 more to 111 more)	⊕⊕⊕O MODERATE	CRITICAL
Mupirocin[1] versus erythromycin[2] - cure or improvement; observer blinded studies only												
2[3]	randomised trials	serious[6]	serious[7]	no serious indirectness	serious[8]	none	65/68 (95.6%)	57/69 (82.6%)	RR 1.12 (0.86 to 1.46)	99 more per 1000 (from 116 fewer to 380 more)	⊕OOO VERY LOW	CRITICAL
Mupirocin[1] versus erythromycin[2] - gastrointestinal adverse events												
4[3]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/152 (5.3%)	28/145 (19.3%)	RR 0.30 (0.14 to 0.60)[10]	135 fewer per 1000 (from 77 fewer to 166 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Mupirocin[1] versus cefalexin[11] - cure or improvement												
1[3]	randomised trials	serious[9]	NA	no serious indirectness	very serious[12]	none	6/7 (85.7%)	9/10 (90.0%)	RR 0.95 (0.66 to 1.37)	45 fewer per 1000 (from 306 fewer to 333 more)	⊕OOO VERY LOW	CRITICAL
Mupirocin[1] versus cefalexin[11] - cure or improvement (secondary impetigo, all eczema)												
1[3]	randomised trials	serious[9]	NA	no serious indirectness	serious[8]	none	52/82 (63.4%)	44/77 (57.1%)	RR 1.11 (0.86 to 1.43)	63 more per 1000 (from 80 fewer to 246 more)	⊕⊕OO LOW	CRITICAL
Mupirocin[1] versus cefalexin[11] – diarrhoea (secondary impetigo, all eczema)												
1[3]	randomised trials	serious[9]	NA	no serious indirectness	very serious[12]	none	2/82 (2.4%)	3/77 (3.9%)	RR 0.63 (0.11 to 3.65)	14 fewer per 1000 (from 35 fewer to 103 more)	⊕OOO VERY LOW	CRITICAL
Mupirocin[1] versus ampicillin[13] - cure or improvement												
1[3]	randomised trials	serious[9]	NA	no serious indirectness[5]	very serious[12]	none	8/9 (88.9%)	2/4 (50.0%)	RR 1.78 (0.65 to 4.87)	390 more per 1000 (from 175 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Fusidic acid[14] versus erythromycin[2] - cure or improvement (bullous impetigo)												
1[3]	randomised trials	serious[9]	NA	no serious indirectness	serious[8]	none	10/12 (83.3%)	7/12 (58.3%)	RR 1.43 (0.83 to 2.45)	251 more per 1000 (from 99 fewer to 846 more)	⊕⊕OO LOW	CRITICAL
Neomycin/bacitracin[15] versus erythromycin[2] - cure or improvement (bullous impetigo)												
1[3]	randomised trials	serious[9]	NA	serious[16]	serious[17]	none	1/12 (8.3%)	7/12 (58.3%)	RR 0.14 (0.02 to 0.99)	502 fewer per 1000 (from 6 fewer to 572 fewer)	⊕OOO VERY LOW	CRITICAL
Chloramphenicol[18] versus erythromycin[2] - cure or improvement (bullous impetigo)												
1[3]	randomised trials	serious[9]	NA	no serious indirectness	serious[17]	none	2/12 (16.7%)	7/12 (58.3%)	RR 0.29 (0.07 to 1.10)	414 fewer per 1000 (from 542 fewer to 58 more)	⊕⊕OO LOW	CRITICAL

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

[1] Topical mupirocin - 2% 3 times daily for 5 to 10 days
[2] Oral erythromycin - 30 to 50 mg/kg/day in 2 to 4 daily doses for 7 to 10 days, 250mg 4 times daily for 7 days, or dose not reported
[3] Koning et al. 2012
[4] Downgraded 1 level - 9 of 10 studies deemed at high risk of bias in 1 or more domains by systematic review authors
[5] Not downgraded – 1 or more studies includes a range of skin infections, with subgroups for impetigo described separately and reported here
[6] Downgraded 1 level - 2 of 2 studies deemed at high risk of bias in 1 or more domain by systematic review authors
[7] Downgraded 1 level – heterogeneity >50%

[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 topical antibiotics
[9] Downgraded 1 level – 1 or more studies deemed at high risk of bias in 1 or more domains by systematic review authors
[10] NICE analysis - meta-analysis not presented within systematic review and calculated by NICE
[11] Oral cefalexin – 50 mg/kg/day in 3 daily doses for 10 days or 250 mg 4 times daily for 10 days
[12] 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
[13] Oral ampicillin - 50 mg 4 times daily for 5 to 10 days
[14] Topical fusidic acid – 2% 3 times daily for 10 days
[15] Topical neomycin/bacitracin ointment – 3 times daily for 10 days
[16] Downgraded 1 level - topical neomycin is classed as a product that is less than suitable for prescribing
[17] 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 oral antibiotic
[18] Topical chloramphenicol ointment – 3 times daily for 10 days

H.5.2 Intramuscular antibiotic compared with oral antibiotic

Table 28: GRADE profile – intramuscular ceftriaxone compared with oral cefadroxil

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intramuscular ceftriaxone[1,2]	Oral cefadroxil[2, 3]	Relative (95% CI)	Absolute		
Cure (day 8)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	no serious imprecision	none	25/25 (100%)	24/24 (100%)	RR 1.00 (0.93 to 1.08)	0 fewer per 1000 (from 70 fewer to 80 more)	⊕⊕⊕O MODERATE	CRITICAL
Cure/excellent response (day 3)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[6]	none	22/25 (88.0%)	20/24 (83.3%)	RR 1.06 (0.84 to 1.33)	50 more per 1000 (from 133 fewer to 275 more)	⊕⊕OO LOW	CRITICAL
Improved response (day 3)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[7]	none	3/25 (12.0%)	4/24 (16.7%)	RR 0.72 (0.18 to 2.89)	47 fewer per 1000 (from 137 fewer to 315 more)	⊕OOO VERY LOW	CRITICAL
Failure to respond (day 3)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[8]	none	0/25 (0%)	0/24 (0%)	-	-	⊕⊕OO LOW	CRITICAL
Relapse (1 month)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[8]	none	0/25 (0%)	0/24 (0%)	-	-	⊕⊕OO LOW	CRITICAL

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

[1] Single dose intramuscular ceftriaxone injection - 50 mg/kg/day
[2] Both intervention and control groups also received topical fusidic acid cream (20g) mixed with hydrocortisone cream (5g; 1%) and were advised to use antibacterial soap to clean infected areas for 7 days
[3] Cefadroxil suspension - 30 mg/kg/day twice daily for 7 days
[4] Al-Samman et al. 2014
[5] Downgraded 1 level - participants could not be blinded due to nature of intervention, however there is no report of an attempt to blind outcome assessors. Lack of blinding may have impacted the outcome assessment.
[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 benefit with ceftriaxone
[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 – small sample size (imprecision not assessable based on relative risk increase [RRI]/reduction [RRR] due to 0 events in each arm)

Table 29: GRADE profile – intramuscular benzylpenicillin compared with oral co-trimoxazole

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intramuscular benzathine benzylpenicillin[1]	Oral co-trimoxazole[2]	Relative (95% CI)	Absolute		
Treatment success - intention to treat (day 7)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision[5]	none	133/156 (85.3%)	283/334 (84.7%)	RR 1.01 (0.93 to 1.09)[6,7]	8 more per 1000 (from 59 fewer to 76 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment success - per protocol (day 7)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision[8]	none	124/146 (84.9%)	264/310 (85.2%)	RR 1.00 (0.92 to 1.08)[7]	0 fewer per 1000 (from 68 fewer to 68 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical success (day 7)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision[5]	none	154/156 (98.7%)	332/334 (99.4%)	RR 0.99 (0.97 to 1.01)[7,9]	10 fewer per 1000 (from 30 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
Resolution of sores from whole body (day 7)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[5, 10]	none	132/155 (85.2%)	296/333 (88.9%)	RR 0.96 (0.89 to 1.03)[7, 11]	36 fewer per 1000 (from 98 fewer to 27 more)	⊕⊕OO LOW	CRITICAL
Treatment success (day 2)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[8, 12]	none	82/155 (52.9%)	166/335 (49.6%)	RR 1.07 (0.89 to 1.28)[7]	35 more per 1000 (from 55 fewer to 139 more)	⊕⊕OO LOW	CRITICAL
Clinical success (day 2)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision[8]	none	117/156 (75%)	233/335 (69.6%)	RR 1.08 (0.96 to 1.21)[7]	56 more per 1000 (from 28 fewer to 146 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[8, 13]	none	49/160 (30.6%)	5/343 (1.5%)	RR 21.01 (8.53 to 51.72)[7]	292 more per 1000 (from 110 more to 739 more)	⊕⊕OO LOW	CRITICAL

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

[1] Benzathine penicillin received as a weight-banded intramuscular injection into the thigh or buttock (weight band </=6 kg, dose 225 mg; 6.1 - 10 kg, 337.5 mg; 10.1 - 15 kg, 450 mg; 15.1 - 20 kg, 675 mg; >20 kg, 900 mg [1.2 million units])
[2] Oral co-trimoxazole 4 mg/kg plus 20 mg/kg (maximum 160 mg plus 800 mg) twice daily for 3 days (3 day course), or oral co-trimoxazole 8 mg/kg plus 40 mg/kg (maximum 320 mg plus 1600 mg) daily for 5 days (5 day course)
[3] Bowen et al. 2014
[4] Downgraded 1 level - study conducted in an aboriginal community, where impetigo prevalence is higher than prevalence in the UK, therefore response to antibiotic treatment may be different in the local population
[5] Imprecision judged using minimal important difference of 10% relative risk increase (RRI)/reduction (RRR), based on non-inferiority margin of 10% and negligible difference between absolute and relative risk ratios
[6] Absolute difference of 0.5%, 95% CI -6.2 to 7.3; 10% non-inferiority margin
[7] NICE analysis – RR calculated from raw data
[8] Imprecision judged using minimal important difference of 25% relative risk increase (RRI)/reduction (RRR) as non-inferiority margin does not apply to this outcome or absolute difference not reported
[9] Absolute difference of -0.7, 95% CI -2.6 to 1.3; 10% non-inferiority margin
[10] Downgraded 1 level – at a minimal important difference of 10% relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with oral co-trimoxazole
[11] Absolute difference of -3.7, 95% CI -10.2 to 2.8; 10% non-inferiority margin
[12] 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 intramuscular benzathine benzylpenicillin
[13] Downgraded 1 level – very wide confidence intervals

Appendix I: Studies not prioritised

Bowen Asha C, Carapetis Jonathan R, Currie Bart J, Fowler Vance Jr, Chambers Henry F, and Tong Steven Y. C (2017) Sulfamethoxazole-Trimethoprim (Cotrimoxazole) for Skin and Soft Tissue Infections Including Impetigo, Cellulitis, and Abscess. Open forum infectious diseases 4(4), ofx232

Bucko Alicia D, Hunt Barbara J, Kidd Sarah L, and Hom Richard (2002) Randomized, double-blind, multicenter comparison of oral cefditoren 200 or 400 mg BID with either cefuroxime 250 mg BID or cefadroxil 500 mg BID for the treatment of uncomplicated skin and skin-structure infections. Clinical therapeutics 24(7), 1134-47

Chamny Shlomo, Miron Dan, Lumelsky Nadia, Shalev Hana, Gazal Elana, Keynan Rita, Shemer Avner, and Tamarkin Dov (2016) Topical Minocycline Foam for the Treatment of Impetigo in Children: Results of a Randomized, Double-Blind, Phase 2 Study. Journal of drugs in dermatology: JDD 15(10), 1238-1243

Edge Rob, and Argaez Charlene (2017) Topical Antibiotics for Impetigo: A Review of the Clinical Effectiveness and Guidelines Tarshis G A, Miskin B M, Jones T M, Champlin J, Wingert K J, Breen J D, and Brown M J (2001) Once-daily oral gatifloxacin versus oral levofloxacin in treatment of uncomplicated skin and soft tissue infections: double-blind, multicenter, randomized study. Antimicrobial agents and chemotherapy 45(8), 2358-62

Appendix J: Excluded studies

Study reference	Reason for exclusion
Agarwal R, Bartsch S M, Kelly B J, Prewitt M, Liu Y, Chen Y, and Umscheid C A (2018) Newer glycopeptide antibiotics for treatment of complicated skin and soft tissue infections: systematic review, network meta-analysis and cost analysis. Clinical Microbiology and Infection 24(4), 361-368	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Aikawa Naoki, Kusachi Shinya, Mikamo Hiroshige, Takesue Yoshio, Watanabe Shinichi, Tanaka Yoshiyuki, Morita Akiko, Tsumori Keiko, Kato Yoshiaki, and Yoshinari Tomoko (2013) Efficacy and safety of intravenous daptomycin in Japanese patients with skin and soft tissue infections. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 19(3), 447-55	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Arbeit Robert D, Maki Dennis, Tally Francis P, Campanaro Edward, Eisenstein Barry I, Daptomycin , and Investigators (2004) The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 38(12), 1673-81	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Bally Michele, Dendukuri Nandini, Sinclair Alison, Ahern Stephane P, Poisson Michel, and Brophy James (2012) A network meta-analysis of antibiotics for treatment of hospitalised patients with suspected or proven meticillin-resistant Staphylococcus aureus infection. International journal of antimicrobial agents 40(6), 479-95	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Beibei Liang, Yun Cai, Mengli Chen, Nan Bai, Xuhong Yu, and Rui Wang (2010) Linezolid versus vancomycin for the treatment of gram-positive bacterial infections: meta-analysis of randomised controlled trials. International journal of antimicrobial agents 35(1), 3-12	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Bliziotis Ioannis A, Plessa Eleni, Peppas George, and Falagas Matthew E (2010) Daptomycin versus other antimicrobial agents for the treatment of skin and soft tissue infections: a meta-analysis. The Annals of pharmacotherapy 44(1), 97-106	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Bounthavong M, Hsu D I, and Okamoto M P (2009) Cost-effectiveness analysis of linezolid vs. vancomycin in treating methicillin-resistant Staphylococcus aureus complicated skin and soft tissue infections using a decision analytic model. International journal of clinical practice 63(3), 376-86	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Bounthavong Mark, and Hsu Donald I (2010) Efficacy and safety of linezolid in methicillin-resistant Staphylococcus aureus (MRSA) complicated skin and soft tissue infection (cSSTI): a meta-analysis. Current medical research and opinion 26(2), 407-21	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Bowen Asha C, Carapetis Jonathan R, Currie Bart J, Fowler Vance Jr, Chambers Henry F, and Tong Steven Y. C (2017) Sulfamethoxazole-Trimethoprim (Cotrimoxazole) for Skin and Soft Tissue Infections Including Impetigo, Cellulitis, and Abscess. Open forum infectious diseases 4(4), ofx232	Excluded on duplication
Cada D J, Levien T, and Baker D E (2007) Retapamulin 1% ointment. Hospital Pharmacy 42(9), 846-852	Excluded - not available
Cenizal M J, Skiest D, Luber S, Bedimo R, Davis P, Fox P, Delaney K, and Hardy R D (2007) Prospective randomized trial of empiric therapy with trimethoprim- sulfamethoxazole or	Excluded on population - either not impetigo or a mixed population of impetigo and

Study reference	Reason for exclusion
doxycycline for outpatient skin and soft tissue infections in an area of high prevalence of methicillin-resistant Staphylococcus aureus. Antimicrobial Agents and Chemotherapy 51(7), 2628-2630	other infections which could not be stratified by population
Chosidow O, Bernard P, Berbis P, Humbert P, Crickx B, Jarlier V, and Group Orpic Study Investigator (2005) Cloxacillin versus pristinamycin for superficial pyodermas: a randomized, open-label, non-inferiority study. Dermatology (Basel, and Switzerland) 210(4), 370-4	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Chuang Y C, Chang C M, Aradhya S, Nagari B, Pai V, Dartois N, Jouve S, and Cooper A (2011) Efficacy and safety of tigecycline monotherapy compared with vancomycin-aztreonam in the treatment of complicated skin and skin structure infections in patients from India and Taiwan. Journal of Microbiology, and Immunology and Infection 44(2), 116-124	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Ciftci Ergin, Guriz Haluk, and Aysev Ahmet Derya (2002) Mupirocin vs terbinafine in impetigo. Indian journal of pediatrics 69(8), 679-82	Excluded as included in a prioritised systematic review
Claudy A (2001) Superficial pyoderma requiring oral antibiotic therapy: fusidic acid versus pristinamycin]. Presse medicale (paris, and france : 1983) 30(8), 364-368	Excluded on non-English language
Corey G Ralph, Good Samantha, Jiang Hai, Moeck Greg, Wikler Matthew, Green Sinikka, Manos Paul, Keech Richard, Singh Rajesh, Heller Barry, Bubnova Natalia, O'Riordan William, and Investigators Solo Ii (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	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Corey G Ralph, Wilcox Mark H, Talbot George H, Thye Dirk, Friedland David, Baculik Tanya, and investigators Canvas (2010) CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. The Journal of antimicrobial chemotherapy 65 Suppl 4, iv41-51	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Corrado Michael L (2010) Integrated safety summary of CANVAS 1 and 2 trials: Phase III, randomized, double-blind studies evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. The Journal of antimicrobial chemotherapy 65 Suppl 4, iv67-iv71	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Covington Paul, Davenport J Michael, Andrae David, O'Riordan William, Liverman Lisa, McIntyre Gail, and Almenoff June (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	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Dalen Dawn, Fry Amy, Campbell Samuel G, Eppler Jeffrey, and Zed Peter J (2018) Intravenous cefazolin plus oral probenecid versus oral cephalexin for the treatment of skin and soft tissue infections: a double-blind, non-inferiority, randomised controlled trial. Emergency medicine journal : EMJ 35(8), 492-498	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Davis S (2015) Impetigo: A review with a focus on retapamulin. SA Pharmaceutical Journal 82(1), 22-25	Excluded on publication/study type - narrative review
Deck D H, Jordan J M, Holland T L, Fan W, Wikler M A, Sulham K A, Ralph Corey, and G (2016) Single-Dose Oritavancin Treatment	Excluded on population - either not impetigo or a mixed

Study reference	Reason for exclusion
of Acute Bacterial Skin and Skin Structure Infections: SOLO Trial Efficacy by Eron Severity and Management Setting. Infectious Diseases and Therapy 5(3), 353-361	population of impetigo and other infections which could not be stratified by population
Dharani Sudha, G , Nirmala P, Ramanathan R, and Samuel V (2017) Comparative study of efficacy and safety of azithromycin alone and in combination with probiotic in the treatment of impetigo in children. International Journal of Current Pharmaceutical Research 9(6), 52-55	Excluded on intervention
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	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Dryden Matthew, Zhang Yingyuan, Wilson David, Iaconis Joseph P, and Gonzalez Jesus (2016) A Phase III, randomized, controlled, non-inferiority trial of ceftaroline fosamil 600 mg every 8 h versus vancomycin plus aztreonam in patients with complicated skin and soft tissue infection with systemic inflammatory response or underlying comorbidities. The Journal of antimicrobial chemotherapy 71(12), 3575-3584	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Dunn C J, and Peter D (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	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Fabian Timothy C, File Thomas M, Embil John M, Krige Jacobus E. J, Klein Stanley, Rose Andrea, Melnick David, and Soto Norberto E (2005) Meropenem versus imipenem-cilastatin for the treatment of hospitalized patients with complicated skin and skin structure infections: results of a multicenter, randomized, double-blind comparative study. Surgical infections 6(3), 269-82	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Fahimi Jahan, Singh Amandeep, and 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	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Falagas M E, Siempos I I, and Vardakas K Z (2008) Linezolid versus glycopeptide or beta-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomised controlled trials. The Lancet Infectious Diseases 8(1), 53-66	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Falagas Matthew E, Matthaiou Dimitrios K, and Vardakas Konstantinos Z (2006) Fluoroquinolones vs beta-lactams for empirical treatment of immunocompetent patients with skin and soft tissue infections: a meta-analysis of randomized controlled trials. Mayo Clinic proceedings 81(12), 1553-66	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Fish D N (2006) Meropenem in the treatment of complicated skin and soft tissue infections. Therapeutics and Clinical Risk Management 2(4), 401-415	Excluded on publication/study type - narrative review
Forcade Nicolas A, Wiederhold Nathan P, Ryan Laurajo, Talbert Robert L, and Frei Christopher R (2012) Antibacterials as adjuncts to incision and drainage for adults with purulent methicillin-resistant Staphylococcus aureus (MRSA) skin infections. Drugs 72(3), 339-51	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population

Study reference	Reason for exclusion
Fu J, Ye X, Chen C, and Chen S (2013) The Efficacy and Safety of Linezolid and Glycopeptides in the Treatment of Staphylococcus aureus Infections. PLoS ONE 8(3), e58240	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Garau Javier (2006) Management of cSSTIs: the role of daptomycin. Current medical research and opinion 22(11), 2079-87	Excluded on publication/study type - narrative review
George A, and Rubin G (2003) A systematic review and meta-analysis of treatments for impetigo. British Journal of General Practice 53(491), 480-487	Excluded as all included RCTs meeting the review protocol are included in a more recent and comprehensive prioritised systematic review
Graham D R, Lucasti C, Malafaia O, Nichols R L, Holtom P, Perez N Q, McAdams A, Woods G L, Ceesay T P, and Gesser R (2002) Ertapenem once daily versus piperacillin-tazobactam 4 times per day for treatment of complicated skin and skin-structure infections in adults: Results of a prospective, randomized, double-blind multicenter study. Clinical Infectious Diseases 34(11), 1460-1468	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Gropper Savion, Albareda Nuria, Chelius Klaus, Kruger Dawie, Mitha Ismail, Vahed Yacoob, Gani Mashra, Garcia-Alonso Fernando, Ozenoxacin in Impetigo Trial Investigators, and Group (2014) Ozenoxacin 1% cream in the treatment of impetigo: a multicenter, randomized, placebo- and retapamulin-controlled clinical trial. Future microbiology 9(9), 1013-23	Excluded as included in an included pooled-analysis
Guay D R. P (2006) Moxifloxacin in the treatment of skin and skin structure infections. Therapeutics and Clinical Risk Management 2(4), 417-434	Excluded on publication/study type - narrative review
Guo Z, Lin Z, Huang P, and Chen Q (2011) Linezolid versus glycopeptides in the treatment of complicated skin and soft tissue infections: A meta-analysis of randomized controlled trials. Chinese Journal of Infection and Chemotherapy 11(4), 268	Excluded - not available
Hanretty A M, and Gallagher J C (2018) Shortened Courses of Antibiotics for Bacterial Infections: A Systematic Review of Randomized Controlled Trials. Pharmacotherapy 38(6), 674-687	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Hebert Adelaide A, Albareda Nuria, Rosen Theodore, Torrelo Antonio, Grimalt Ramon, Rosenberg Noah, Zsolt Ilonka, and Masramon Xavier (2018) Topical Antibacterial Agent for Treatment of Adult and Pediatric Patients With Impetigo: Pooled Analysis of Phase 3 Clinical Trials. Journal of drugs in dermatology : JDD 17(10), 1051-1057	Excluded on duplication
Hirschmann J V (2002) Impetigo: etiology and therapy. Current clinical topics in infectious diseases 22, 42-51	Excluded on publication/study type - narrative review
Hood R, Shermock K M, and Emerman C (2004) A Prospective, Randomized Pilot Evaluation of Topical Triple Antibiotic Versus Mupirocin for the Prevention of Uncomplicated Soft Tissue Wound Infection. American Journal of Emergency Medicine 22(1), 1-3	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Ibrahim F, Khan T, and Pujalte G G. A (2015) Bacterial Skin Infections. Primary Care - Clinics in Office Practice 42(4), 485-499	Excluded on publication/study type - not a research study
Ioannidou M, Apostolidou-Kiouti F, Haidich A B, Niopas I, and Roilides E (2014) Efficacy and safety of linezolid for the treatment	Excluded on population - either not impetigo or a mixed population of impetigo and

Study reference	Reason for exclusion
of infections in children: A meta-analysis. European Journal of Pediatrics 173(9), 1179-1186	other infections which could not be stratified by population
Iovino Susan M, Krantz Kenneth D, Blanco Daisy M, Fernandez Josefina A, Ocampo Naomi, Najafi Azar, Memarzadeh Bahram, Celeri Chris, Debabov Dmitri, Khosrovi Behzad, and Anderson Mark (2011) NVC-422 topical gel for the treatment of impetigo. International journal of clinical and experimental pathology 4(6), 587-95	Excluded on intervention
Itani Kamal M. F, Biswas Pinaki, Reisman Arlene, Bhattacharyya Helen, and Baruch Alice M (2012) Clinical efficacy of oral linezolid compared with intravenous vancomycin for the treatment of methicillin-resistant Staphylococcus aureus-complicated skin and soft tissue infections: a retrospective, propensity score-matched, case-control analysis. Clinical therapeutics 34(8), 1667-73.e1	Excluded on study type - observational
Itani Kamal M. F, Dryden Matthew S, Bhattacharyya Helen, Kunkel Mark J, Baruch Alice M, and Weigelt John A (2010) Efficacy and safety of linezolid versus vancomycin for the treatment of complicated skin and soft-tissue infections proven to be caused by methicillin-resistant Staphylococcus aureus. American journal of surgery 199(6), 804-16	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Jacobs M R (2010) Retapamulin: Focus on its use in the treatment of uncomplicated superficial skin infections and impetigo. Expert Review of Dermatology 5(5), 505-517	Excluded on publication/study type - narrative review
Jauregui L E, Babazadeh S, Seltzer E, Goldberg L, Krievins D, Frederick M, Krause D, Satilovs I, Endzinas Z, Breaux J, and O'Riordan W (2005) Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. Clinical Infectious Diseases 41(10), 1407-1415	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Johnston Graham A (2004) Treatment of bullous impetigo and the staphylococcal scalded skin syndrome in infants. Expert review of anti-infective therapy 2(3), 439-46	Excluded on publication/study type - narrative review
Kish T D, Chang M H, and Fung H B (2010) Treatment of skin and soft tissue infections in the Elderly: A review. American Journal Geriatric Pharmacotherapy 8(6), 485-513	Excluded on publication/study type - narrative review
Koning S, van der Wouden , J C, Chosidow O, Twynholm M, Singh K P, Scangarella N, and Oranje A P (2008) Efficacy and safety of retapamulin ointment as treatment of impetigo: randomized double-blind multicentre placebo-controlled trial. The British journal of dermatology 158(5), 1077-82	Excluded as included in a prioritised systematic review
Koning Sander, van Suijlekom-Smit , Lisette W A, Nouwen Jan L, Verduin Cees M, Bernsen Roos M. D, Oranje Arnold P, Thomas Siep, van der Wouden , and Johannes C (2002) Fusidic acid cream in the treatment of impetigo in general practice: double blind randomised placebo controlled trial. BMJ (Clinical research ed.) 324(7331), 203-6	Excluded as included in a prioritised systematic review
Koning S, Van Suijlekom-Smit , L , Nouwen J, Verduin C, Bernsen R, Oranje A, Thomas S, Van der Wouden , and H (2002) Fusidic acid ointment for the treatment of impetigo: a double-blind randomized placebo controlled study. Huisarts en wetenschap 45(5), 232-238	Excluded on duplication
Koning S, Verhagen A P, van Suijlekom-Smit , L W, and Larcombe J H (2004) Review: Topical mupirocin or fusidic acid may be more effective than oral antibiotics for limited non-bullous impetigo. Evidence-Based Medicine 9(6), 176	Excluded on publication/study type - commentary

Study reference	Reason for exclusion
Konychev Alexander, Heep Markus, Moritz Rose K. C, Kreuter Alexander, Shulutko Alexander, Fierlbeck Gerhard, Bouylout Kamel, Pathan Rashidkhan, Trostmann Uwe, and Chaves Ricardo L (2013) Safety and efficacy of daptomycin as first-line treatment for complicated skin and soft tissue infections in elderly patients: an open-label, multicentre, randomized phase IIIb trial. Drugs & aging 30(10), 829-36	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Kuniyuki Shuichi, Nakano Kazuhito, Maekawa Naoki, and Suzuki Shinsuke (2005) Topical antibiotic treatment of impetigo with tetracycline. The Journal of dermatology 32(10), 788-92	Excluded as included in a prioritised systematic review
Ladhani S, and Garbash M (2005) Staphylococcal skin infections in children: Rational drug therapy recommendations. Pediatric Drugs 7(2), 77-102	Excluded on publication/study type - narrative review
Lee Su Young, Kuti Joseph L, and Nicolau David P (2005) Antimicrobial management of complicated skin and skin structure infections in the era of emerging resistance. Surgical infections 6(3), 283-95	Excluded on publication/study type - narrative review
Lewis Ii J. S, and Ellis M W (2007) Approaches to serious methicillin-resistant Staphylococcus aureus infections with decreased susceptibility to vancomycin: Clinical significance and options for management. Current Opinion in Infectious Diseases 20(6), 568-573	Excluded on publication/study type - narrative review
Li J Z, Willke R J, Rittenhouse B E, and Rybak M J (2003) Effect of linezolid versus vancomycin on length of hospital stay in patients with complicated skin and soft tissue infections caused by known or suspected methicillin-resistant staphylococci: Results from a randomized clinical trial. Surgical Infections 4(1), 57-70	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Li Yan, and Xu Wei (2018) Efficacy and safety of linezolid compared with other treatments for skin and soft tissue infections: a meta-analysis. Bioscience reports 38(1),	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Li Z, Willke R J, Pinto L A, Rittenhouse B E, Rybak M J, Pleil A M, Crouch C W, Hafkin B, and Glick H A (2001) Comparison of length of hospital stay for patients with known or suspected methicillin-resistant Staphylococcus species infections treated with linezolid or vancomycin: A randomized, multicenter trial. Pharmacotherapy 21(3 I), 263-274	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Lin Dong-Fang, Zhang Ying-Yuan, Wu Ju-Fang, Wang Fu, Zheng Jing-Chuan, Miao Jing-Zhi, Zheng Li-Ye, Sheng Rui-Yuan, Zhou Xin, Shen Hua-Hao, Ijzerman Margaret Marian, Croos-Dabrera Rodney Victor, and Sheng Wei (2008) Linezolid for the treatment of infections caused by Gram-positive pathogens in China. International journal of antimicrobial agents 32(3), 241-9	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Liu C, Mao Z, Yang M, Kang H, Liu H, Pan L, Hu J, Luo J, and Zhou F (2016) Efficacy and safety of daptomycin for skin and soft tissue infections: A systematic review with trial sequential analysis. Therapeutics and Clinical Risk Management 12, 1455-1466	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Logman J Floris S, Stephens Jennifer, Heeg Bart, Haider Seema, Cappelleri Joseph, Nathwani Dilip, Tice Alan, van Hout , and Ben A (2010) Comparative effectiveness of antibiotics for the treatment of MRSA complicated skin and soft tissue infections. Current medical research and opinion 26(7), 1565-78	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Marks Michael, Toloka Hilary, Baker Ciara, Kositz Christian, Asugeni James, Puiahi Elliot, Asugeni Rowena, Azzopardi Kristy,	Excluded on population - either not impetigo or a mixed

Study reference	Reason for exclusion
Diau Jason, Kaldor John M, Romani Lucia, Redman-MacLaren Michelle, MacLaren David, Solomon Anthony W, Mabey David C. W, and Steer Andrew C (2018) Randomised trial of community treatment with azithromycin and ivermectin mass drug administration for control of scabies and impetigo. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America ,	population of impetigo and other infections which could not be stratified by population
Matthews P, Alpert M, Rahav G, Rill D, Zito E, Gardiner D, Pedersen R, Babinchak T, McGovern P C, Armstrong P, Bailey C, Berbel G, Bernstein J, Bordon J, Bruno-Murtha L A, Caprioli R, Casey K, Chiang T, Churukian A, Flynn W, Graham D, Hao Z, Kalassian K, Kohler R, Lee J, Leeds W, Lucasti C, Malanoski G, Ko T, Minnaganti V, Mogyoros M, Morgan B, Moss C, Muluk S, Murthy R, O'Riordan W, Pien F, Polk H, Augustinsky J B, Salvaggio M, Smith L, Smith R, Scott Stienecker, R , Suh B, Vazquez J, Weiland D E, Wessolossky M, Zenilman J, Abraham C, Nathan R, Sanchez P, Baird I, Callahan C, Schrock C G, Lau W, Bochan M R, Somero M, Klein S R, Bellows C, D'Hooghe A, Ceulemans F, Gaillat J, Garo B, Eckmann C, Haier J, Suter F, Bertani A, Acin F, Jimenez-Mejias M E, Blanes I, Regueiro D S, Cakir N, Saba R, Giladi M, Kanj-Sharara S, Ahmed al Thaqafi, A O, Ng W M, Burd A, Kurlekar U, Rao N R, Devarajan T, Choi J, Kim Y, Pai H, Park Y S, Kumar S, Chow T S, Crisostomo A, Erasmo A, Low J, Basson , Breedt J, Matthews , Ross D P, Lin H H, Liao C H, Kung H C, Chinswangwatanakul V, Malathum K, Tantawichien T, Sergio Ricardo Filho, Penteado , Cardoso F, Gomez R F, Velazquez D F, Tinoco-Favila J C, Poirier A, Valiquette L, Weiss K, Grimard D, Embil J M. A, Sanche S E, Smith K, Chouinard S, and Dolce P (2012) A randomized trial of tigecycline versus ampicillin-sulbactam or amoxicillin-clavulanate for the treatment of complicated skin and skin structure infections. BMC Infectious Diseases 12, 297	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Mikamo Hiroshige, Takesue Yoshio, Iwamoto Yuji, Tanigawa Takahiko, Kato Masaharu, Tanimura Yoko, and Kohno Shigeru (2018) Efficacy, safety and pharmacokinetics of tedizolid versus linezolid in patients with skin and soft tissue infections in Japan - Results of a randomised, multicentre phase 3 study. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 24(6), 434-442	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Montravers Philippe, Bassetti Matteo, Dupont Herve, Eckmann Christian, Heizmann Wolfgang R, Guirao Xavier, Garcia Miguel Sanchez, Capparella Maria Rita, Simoneau Damien, and Bodmann Klaus Friedrich (2013) Efficacy of tigecycline for the treatment of complicated skin and soft-tissue infections in real-life clinical practice from five European observational studies. The Journal of antimicrobial chemotherapy 68 Suppl 2, ii15-24	Excluded on publication/study type - observational
Nolting K S, and Ulbricht H M (2003) Antibacterial efficacy of an antimycotic: a double-blind study of ciclopiroxolamine versus gentamicin. Haut 14(3), 115-117	Excluded - not available
Oranje Arnold P, Chosidow Olivier, Sacchidanand Sarvajnamurthy, Todd Gail, Singh Krishan, Scangarella Nicole, Shawar Ribhi, Twynholm Monique, and Team T O. C. Study (2007) Topical retapamulin ointment, 1%, versus sodium fusidate ointment, 2%, for impetigo: a randomized, observer-blinded, noninferiority study. Dermatology (Basel, and Switzerland) 215(4), 331-40	Excluded as included within a prioritised systematic review

Study reference	Reason for exclusion
O'Riordan W, McManus A, Teras J, Poromanski I, Cruz-Saldariagga M, Quintas M, Lawrence L, Liang S, and Cammarata S (2018) A Comparison of the Efficacy and Safety of Intravenous Followed by Oral Delafloxacin with Vancomycin Plus Aztreonam for the Treatment of Acute Bacterial Skin and Skin Structure Infections: A Phase 3, Multinational, Double-Blind, Randomized Study. Clinical Infectious Diseases 67(5), 657-666	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Pangilinan Ronald, Tice Alan, and Tillotson Glenn (2009) Topical antibiotic treatment for uncomplicated skin and skin structure infections: review of the literature. Expert review of anti-infective therapy 7(8), 957-65	Excluded as all included RCTs meeting the review protocol are included in a more recent and comprehensive prioritised systematic review
Pereira Luciana Baptista (2014) Impetigo - review. Anais brasileiros de dermatologia 89(2), 293-9	Excluded on publication/study type - narrative review
Pierard-Franchimont C, Henry F, Szepetiuk G, Devillers C, and Pierard G E (2008) Comparative randomized intraindividual assessment of the efficacy of fusidic acid and povidone iodine in impetigo. Current Topics in Pharmacology 12(2), 113-117	Excluded - not available
Polyzos K A, Mavros M N, Vardakas K Z, Makris M C, Rafailidis P I, and Falagas M E (2012) Efficacy and safety of telavancin in clinical trials: A systematic review and meta-analysis. PLoS ONE 7(8), e41870	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Quist S R, Fierlbeck G, Seaton R A, Loeffler J, and Chaves R L (2012) Comparative randomised clinical trial against glycopeptides supports the use of daptomycin as first-line treatment of complicated skin and soft-tissue infections. International journal of antimicrobial agents 39(1), 90-91	Excluded on study type- letter
Raghavan Murugan, and Linden Peter K (2004) Newer treatment options for skin and soft tissue infections. Drugs 64(15), 1621-42	Excluded on publication/study type - narrative review
Rajendran P M, Young D, Maurer T, Chambers H, Perdreau-Remington F, Ro P, and Harris H (2007) Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community-acquired methicillin-resistant Staphylococcus aureus infection. Antimicrobial Agents and Chemotherapy 51(11), 4044-4048	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Roberts S A, and Lang S D. R (2000) Skin and soft tissue infections. New Zealand Medical Journal 113(1109), 164-167	Excluded on publication/study type - narrative review
Scheinfeld N S (2007) Skin disorders in elderly persons: Part 3, bacterial diseases. Consultant 47(2), 177-186	Excluded on publication/study type - not a research study
Schofer H, and Simonsen L (2010) Fusidic acid in dermatology: An updated review. European Journal of Dermatology 20(1), 6-15	Excluded on publication/study type - observational
Seltzer Elyse, Dorr Mary Beth, Goldstein Beth P, Perry Marc, Dowell James A, Henkel Tim, Dalbavancin Skin, Soft-Tissue Infection Study, and Group (2003) Once-weekly dalbavancin versus standard-of-care antimicrobial regimens for treatment of skin and soft-tissue infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 37(10), 1298-303	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Sharpe J Neal, Shively Eugene H, Polk Hiram C, and Jr (2005) Clinical and economic outcomes of oral linezolid versus intravenous vancomycin in the treatment of MRSA-complicated, lower-extremity skin and soft-tissue infections caused by	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population

Study reference	Reason for exclusion
methicillin-resistant Staphylococcus aureus. American journal of surgery 189(4), 425-8	
Siami Flora S, LaFleur Bonnie J, and Siami Ghodrat A (2002) Clinafloxacin versus piperacillin/tazobactam in the treatment of severe skin and soft-tissue infections in adults at a Veterans Affairs medical center. Clinical therapeutics 24(1), 59-72	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Stevens D L, Smith L G, Bruss J B, McConnell-Martin M A, Duvall S E, Todd W M, and Hafkin B (2000) Randomized comparison of linezolid (PNU-100766) versus oxacillin-dicloxacillin for treatment of complicated skin and soft tissue infections. Antimicrobial agents and chemotherapy 44(12), 3408-13	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Stryjewski Martin E, O'Riordan William D, Lau William K, Pien Francis D, Dunbar Lala M, Vallee Marc, Fowler Vance G, Jr , Chu Vivian H, Spencer Elizabeth, Barriere Steven L, Kitt Michael M, Cabell Christopher H, Corey G Ralph, and Group Fast Investigator (2005) Telavancin versus standard therapy for treatment of complicated skin and soft-tissue infections due to gram-positive bacteria. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 40(11), 1601-7	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Talan D A, Summanen P H, and Finegold S M (2000) Ampicillin/sulbactam and cefoxitin in the treatment of cutaneous and other soft-tissue abscesses in patients with or without histories of injection drug abuse. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 31(2), 464-71	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Tanus Tonny, Scangarella-Oman Nicole E, Dalessandro Marybeth, Li Gang, Breton John J, and Tomayko John F (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	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
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	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Van Der Wouden Jcet, and al (2002) Fusidic acid cream versus placebo in the treatment of impetigo Abstract. Annales de dermatologie ET de venereologie , IC0676	Excluded on study type - abstract only
Vardakas K Z, Mavros M N, Roussos N, and Falagas M E (2012) Meta-analysis of randomized controlled trials of vancomycin for the treatment of patients with gram-positive infections: Focus on the study design. Mayo Clinic Proceedings 87(4), 349-363	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Vidal L, Borok S, Gafter-Gvili A, Fraser A, Leibovici L, and Paul M (2007) Aminoglycosides as a single antibiotic versus other (non-aminoglycosides) antibiotics for the treatment of patients with infection. Cochrane Database of Systematic Reviews (2), CD006485	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Wang Shou Zhen, Hu Jun Tao, Zhang Chi, Zhou Wei, Chen Xian Feng, Jiang Liang Yan, and Tang Zhan Hong (2014) The safety and efficacy of daptomycin versus other antibiotics for skin and soft-tissue infections: a meta-analysis of randomised controlled trials. BMJ open 4(6), e004744	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population

Study reference	Reason for exclusion
Wasilewski M M, Wilson M G, Sides G D, and Stotka J L (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	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
White B, and Seaton R A (2011) Complicated skin and soft tissue infections: Literature review of evidence for and experience with daptomycin. Infection and Drug Resistance 4(1), 115-127	Excluded on publication/study type - narrative review
Wilcox Mark H, Corey G Ralph, Talbot George H, Thye Dirk, Friedland David, Baculik Tanya, and investigators Canvas (2010) CANVAS 2: the second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. The Journal of antimicrobial chemotherapy 65 Suppl 4, iv53-iv65	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Wren Christopher, Bell Edward, and Eiland Lea S (2018) Ozenoxacin: A Novel Topical Quinolone for Impetigo. The Annals of pharmacotherapy 52(12), 1233-1237	Excluded on publication/study type - narrative review
Yang Lily P. H, and Keam Susan J (2008) Retapamulin: a review of its use in the management of impetigo and other uncomplicated superficial skin infections. Drugs 68(6), 855-73	Excluded on publication/study type - narrative review
Yue Jirong, Dong Bi Rong, Yang Ming, Chen Xiaomei, Wu Taixiang, and Liu Guan J (2013) Linezolid versus vancomycin for skin and soft tissue infections. The Cochrane database of systematic reviews (7), CD008056	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population
Yue Jirong, Dong Bi Rong, Yang Ming, Chen Xiaomei, Wu Taixiang, and Liu Guan J (2016) Linezolid versus vancomycin for skin and soft tissue infections. The Cochrane database of systematic reviews (1), CD008056	Excluded on population - either not impetigo or a mixed population of impetigo and other infections which could not be stratified by population

Appendix K: Research recommendations

1. For which people with impetigo are antiseptics as effective as antibiotics?

Limited evidence was identified comparing hydrogen peroxide cream to antibiotics for the treatment of impetigo. Based on the evidence and their experience, the committee was able to make a recommendation to consider hydrogen peroxide 1% cream in people with localised non-bullous impetigo and to offer a short course of a topical antibiotic if this is not suitable.

Further research is needed to answer in which specific populations antiseptics are as effective as antibiotics. People who will equally benefit from an antiseptic compared to an antibiotic should be offered an antiseptic to help reduce the occurrence of adverse events and help limit antibiotic resistance. The only evidence identified on antiseptics was for hydrogen peroxide. Therefore, further evidence on antiseptics should use a variety of antiseptic treatments and stratify results based on antiseptic used.

PICO	**Population:** People with impetigo (including localised and non-localised impetigo) **Interventions:** Topical antiseptic **Comparator:** Topical antibiotic **Outcomes:** Time to resolution (follow-up for 21 days) Number of people with change of treatment (reported by group) Adverse events
Current evidence base	1 SR and 2 RCTs
Study design	Randomised controlled trial
Other comments	Studies should be adequately powered. Study should be a non-inferiority trial. Results should be stratified by population (localised and non-localised impetigo; number of lesions) and type of antiseptic.