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Antibiotics for uncomplicated skin abscesses: systematic review and network meta-analysis

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Abstract

Objective

To assess the impact of adjunctive antibiotic therapy on uncomplicated skin abscesses.

Design

Systematic review and network meta-analysis.

Data sources

Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov.

Study selection

A BMJ Rapid Recommendation panel provided input on design, important outcomes and the interpretation of the results. Eligible RCTs included a comparison of antibiotics against no antibiotics or a comparison of different antibiotics in patients with uncomplicated skin abscesses, and reported outcomes pre-specified by the linked guideline panel.

Review methods

Reviewers independently screened abstracts and full texts for eligibility, assessed risk of bias and extracted data. We performed random-effects

meta-analyses that compared antibiotics to no antibiotics, along with a limited number of pre-specified subgroup hypotheses. We also performed network meta-analysis with a Bayesian framework to compare effects of different antibiotics. Quality of evidence was assessed with the GRADE approach.

Results

Fourteen RCTs including 4,198 patients proved eligible. Compared to no antibiotics, antibiotics probably lower the risk of treatment failure (odds ratio (OR) 0.58, 95% CI 0.37 to 0.90; low quality), recurrence within 1 month (0.48, 0.30 to 0.77; moderate quality), hospitalization (0.55, 0.32 to 0.94; moderate quality), and late recurrence (0.64, 0.48 to 0.85; moderate quality). However, relative to no use, antibiotics probably increase the risk of gastrointestinal side effects (TMP-SMX: 1.28, 1.04 to 1.58; moderate quality; clindamycin: 2.29, 1.35 to 3.88; high quality) and diarrhoea (clindamycin: 2.71, 1.50 to 4.89; high quality). Cephalosporins did not reduce the risk of treatment failure compared to placebo (moderate quality).

Conclusions

In patients with uncomplicated skin abscesses, moderate-to-high quality evidence suggests TMP-SMX or clindamycin confer a modest benefit for several important outcomes, but this is offset by a similar risk of adverse effects. Clindamycin has a substantially higher risk of diarrhoea than TMP-SMX. Cephalosporins are probably not effective.

Article summary

Strengths and limitations of this study

- This review is linked to a BMJ Rapid Recommendations project which aims to make rapid and trustworthy recommendations regarding new research that might change clinical practice.
- We systematically identified and rigorously collected the available evidence to inform choice of antibiotics for uncomplicated skin abscesses. We used the GRADE approach to assess the quality of evidence of estimates derived from pairwire and network meta-analysis.
- Sufficient data were available only for treatment failure and recurrence within 1 month, but not for other outcomes. In addition, limited data about rare adverse events were available in the RCTs.
- Most of included RCTs involved patients treated in an emergency department, limited evidence apply to patients who present to general practice.
- MRSA resistance patterns may differ across sites, individual patient clinical factors, values and preferences are variable as well. The decision whether or not to use antibiotics should take into account these importance factors.

Introduction

Skin and soft tissue infections (SSTIs) are common, accounting for approximately 5 physician visits per year for every 100 people, for which abscess/cellulitis is most common.[1] Hospital admissions for SSTIs appear to be increasingly common[2] possibly because of the high prevalence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA).[3] In the US, approximately 59% of patients with SSTIs were infected with CA-MRSA,[3,4] and CA-MRSA infections has become a global problem.

The appropriate strategies for managing SSTIs, especially those caused by CA-MRSA, are yet to be established. Until now, the role of adjuvant antibiotic therapy in addition to incision and drainage (I&D) has been controversial, [5-7] at least in part because randomised controlled trials (RCTs) have failed to consistently show benefit. A systematic review including five RCTs with 687 patients and seven observational studies with 1336 patients concluded that adjuvant antibiotics may not improve the chance of cure beyond the benefits of I&D alone.[8] Recently, two large RCTs were published, [9,10] both of which suggested that adjunctive trimethoprim and sulfamethoxazole (TMP-SMX) or clindamycin may confer benefits compared to placebo.

Prompted by the BMJ Rapid Recommendation team's suggestions that this new evidence might change clinical practice, we conducted this systematic review to inform a BMJ Rapid Recommendation – a project that aims to make rapid and trustworthy recommendations regarding new research that might change clinical practice.[11] We addressed two clinical questions—in patients with uncomplicated skin abscesses, what is the impact of antibiotic plus I&D compared to I&D alone; and what are the impacts of the different antibiotic options

Methods

We followed the reporting standards set by Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [12] and the PRISMA network meta-analysis extension statement.[13]

Relationship to the BMJ Rapid Recommendation panel

According to the BMJ Rapid Recommendations process,[11] a semi-independent guideline panel provided critical oversight to the review and identified populations, subgroups, and outcomes of interest. The panel included three people with lived experience of skin abscesses, physicians (five general practitioners, two paediatricians, three infectious diseases specialists, a dermatologist and four general internists), and several research methodologists. The panel members helped interpret the evidence in this review and make clinical practice recommendations[14].

Patient involvement

Two adult patients and one parent of a child patient were full panel members of the linked BMJ Rapid Recommendation.[11] They worked with the rest of the panel, with the help of a patient liaison expert, to identify the outcomes that were important for decision-making; they also led the interpretation of the results based on what they expected the typical patient values and preferences to be, as well as the variation between patients.

Eligibility criteria

We included randomised controlled trials (RCTs) that included a comparison of antibiotics versus no antibiotics or a comparison of different types of antibiotics in children or adult patients with uncomplicated skin abscesses, and explicitly reported data on at least one of the outcomes pre-specified by the BMJ Rapid Recommendation guideline panel. Furuncles (boils) and carbuncles were included in the definition of skin abscesses, while pustules and papules were not. No restrictions were applied to types of antibiotics. The pre-specified outcomes included treatment failure, recurrence (at same or different site), hospitalisation, need for an additional surgical procedure, a similar infection in a household member, pain, invasive infections, gastrointestinal side effects, diarrhoea, nausea, death, and anaphylaxis.

Literature search

We searched Medline, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 17 August 2017 to identify relevant studies, without language restrictions. We combined database-specific subject headings (such as MeSH terms) and free-text terms regarding "skin abscess" and "anti-infective agents" to search for potentially eligible studies. We also searched ClinicalTrials.gov to identify any unpublished studies and reviewed the reference lists of the included RCTs. Supplementary Appendix 1 presents the full search strategy.

Study process

Three reviewers (WW, WWC and YML), independently and in duplicate, screened titles/abstracts for potential eligibility and full texts for final eligibility; assessed risk of bias; and collected data from each eligible trial using standardized, pilot tested forms. Reviewers resolved

disagreement through discussion or by adjudication by a third reviewer (LL).

Risk of bias assessment

We assessed risk of bias of RCTs using a modified version of the Cochrane tool, in which we used response options of "definitely or probably yes" (assigned a low risk of bias) and "definitely or probably no" (assigned a high risk of bias), an approach that has been validated.[15-17] The items for the risk of bias tool included random sequence generation; concealment of treatment allocation; blinding of participants, caregivers, and outcome assessors; infrequent missing outcome data.

Data extraction

We collected the following information from each eligible RCT: study characteristics (study design, total number of patients, length of follow up, whether the trial was an international study, number of sites, and stratification by skin abscess if a trial included other populations with infection); patient characteristics (gender, age and infection pathogen, type of abscess, and inclusion criterion); intervention characteristics (surgical treatment for abscess, type of antibiotics used in the treatment group, agents used in control, dose, and duration of treatment); and outcome data (outcomes of interest, events and numbers of patients included for analyses in each group).

Data analysis and rating quality of evidence

For our primary comparison of antibiotics vs. no antibiotics, we conducted pairwise meta-analyses. We used the random-effects

Mantel-Haenszel (M-H) method to estimate odds ratios (ORs) and 95% confidence intervals (CIs). For the outcomes with low event rate (<5%), we pooled data using Peto's method. We examined statistical heterogeneity among studies using the I^2 statistic and Cochran's chi-square test. We used complete case analysis for efficacy outcomes and as treated analysis for safety outcomes as our primary analyses.

We planned, according to the guideline panel's specification, five hypotheses to explain variability in effect estimates between studies: antibiotic MRSA coverage (hypothesizing larger effects with MRSA coverage versus no MRSA coverage), individual antibiotics (hypothesizing smaller effects with TMP-SMX versus clindamycin), type of patients (hypothesizing larger effects with children versus adults), treatment course (hypothesizing smaller effects with <7 days versus ≥7 days), and abscess size (hypothesizing larger effects with ≥5cm versus <5cm). We conducted subgroup analyses if there were at least two trials in each subgroup category.

We conducted the following sensitivity analyses to examine the robustness of effect estimates: analyses using alternative effect measures (odds ratio versus relative risk), statistical models (fixed versus random effects), pooling methods (Peto versus M-H), alternative methods for random effects meta-analysis (DerSimonian and Laird [DL] versus Hartung-Knapp-Sidik-Jonkman [HKSJ]), and alternative assumptions about missing data; as well as analyses omiting trials published before 1990 and trials with patients treated by primary suture rather than open drainage and, for treatment failure, excluding trials that considered recurrences as treatment failure.

We also conducted a network meta-analysis (NMA) of RCTs using a Bayesian approach to compare effects of alternative antibiotics. We fitted a

Bayesian random-effect hierarchical model with non-informative priors and adjusted for correlation between effects in multi-arm trials. We assumed common heterogeneity within the network. We generated posterior samples using Markov Chain Monte Carlo (MCMC) simulation technique running the analysis in three parallel chains. We used 10,000 burn-in simulations to allow convergence and then a further 100,000 simulations to produce the outputs. We assessed model convergence using Gelman and Rubin diagnostic test.[18] The primary network meta-analysis was conducted with uninformative priors with a uniform distribution, Unif(0, 5). We also conducted a sensitivity analysis with weakly informative priors (HN(0, 1)I(0,).

We report pooled ORs for direct, indirect and mixed network meta-analysis estimates and associated 95% credible intervals (CrI). We present the direct, indirect, and network effect estimates. We used the node-splitting approach for the assessment of loop inconsistency in our triangular loop.[19] Finally, we presented pooled risk differences (RD) for all the comparisons. To estimate absolute effect for treatment failure, we used the median baseline risk from the no antibiotics arms and applied it to the relative effect from the network estimates. We performed all analyses with R (R Core Team. 2016. Vienna, Austria: R Foundation for Statistical Computing) using the gemtc library.[20]

We followed the GRADE approach to rate the quality of evidence of estimates derived from pairwire and network meta-analysis.[21,22] Direct evidence from RCTs starts at high quality and can be rated down based on risk of bias, indirectness, imprecision, inconsistency, and publication bias. When the estimates were not robust to the worst plausible analysis, we rated down our certainty in the evidence for risk of bias.[23] For NMA estimates, we rated the quality of evidence in each of the direct, indirect, and NMA estimates.[22] The rating of indirect estimates starts at the

lowest rating of the two pairwise estimates that contribute as first order loops to the indirect estimate but can be rated down further for intransitivity. If direct and indirect estimates contributed similar power to the network estimate, then we used the higher rating. The network estimates were further rated down if they were incoherent.

Results

Our search yielded 4,198 potentially relevant reports and 12[9,10,24-33] ultimately proved eligible (figure 1). One report[29] included two independent RCTs, and the other[28] reported results of a factorial trial that also compared two surgical approaches and reported results separately for each approach. In total, there were 14 RCTs that enrolled a 3,541 patients with uncomplicated skin abscesses (range 1[9] to 1265), of which nine were multicenter studies,[9,10,26,29-33] and five were published prior to the year of 2000.[25,28,31,33] Eleven trails reported study setting, of which nine[9,10,24-26,28,30,32] (n = 3068) were conducted in emergency department, one[33] (n =174) in outpatient dermatology clinics, and the other one[27] in an Integrated Soft Tissue Infection Services (ISIS) clinic involving patients with high rates of comorbidity, such as infection with hepatitis C, hepatitis B, or HIV.

Two trials[25,26] exclusively enrolled adults, two exclusively enrolled children,[24,31] seven included both adults and children, [9,10,29,30,32,33]and three others provided no details.[27,28] Three trials reported abscess size of enrolled patients. [9,10,32] The largest trial[9] specifically focused on small abscesses, in which no patients had signs of systemic infection. Two trials[10,27] included a proportion of patients with diabetes (2.4% to 11%). The most common pathogen cultured was MRSA, the proportion of which ranged from 43.5% to 87.8%. None of the trials reported resistance rates

of clindamycin and TMP-SMX. Ten trials reported surgical treatment for abscess, of which 9 performed incision and drainage [9,10,24-28,30,32] and the other performed incision, curettage, and primary suture[28] (table 1). The descriptions of abscess definitions were summarized in table A of appendix 2.

Antibiotics included TMP-SMX, clindamycin, early cephalosporins, late cephalosporins, and azithromycin. Eight trials [9,10,24-28] compared antibiotics (TMP-SMX, clindamycin, cephradine, cephalexin) to no antibiotics, of which six administered antibiotics for at least 7 days; [9,10,24-27] the two others used clindamycin for 4 days.[28] Six other trials [29-33] examined comparative effects of alternative antibiotics, and the treatment courses ranged from 3 days to 14 days. The length of follow-up ranged from 7 to 90 days across the trials (table 1).

All the 14 trials adequately generated their randomization sequence, 11 (78.6%) concealed treatment allocation, 10 (71.4%) blinded participants, 11 (78.6%) blinded caregivers, 11 (78.6%) blinded outcome assessors, and 6 (42.8%) trials had infrequent missing outcome. (table B in appendix 2).

Effects of antibiotics versus no antibiotics

Eight trials [9,10,24-28] compared antibiotics to no antibiotics. The risk of treatment failure was probably lower in patients randomised to antibiotics (eight trials,[9,10,24-28] OR 0.58, 95% CI 0.37 to 0.90, I^2=48%; risk difference 37 fewer (56 fewer to 9 fewer) per 1000 patients with uncomplicated skin abscess; low quality; figure 2 and table 2). For this outcome, we found sufficient information to conduct three pre-specified subgroup

analyses: analysis by age (≥18 versus < 18 years old) and individual antibiotics (TMP-SMX versus clindamycin) suggested no significant difference (interaction P = 0.36 and 0.95, figures 3 and 4). Antibiotics with activity against MRSA (TMP-SMX and clindamycin) proved more likely to reduce the risk of treatment failure than those without activity against MRSA (first generation cephalosporins) (interaction P=0.008; figure 5; antibiotics with MRSA activity, six trials, [9,10,24,26,28] OR 0.45, 95% CI 0.33 to 0.62 , I^2=13%; high quality; antibiotics without MRSA activity [cephalosporins], two trials,[25,27] OR 1.82, 95% CI 0.68 to 4.85, I^2= 0%; moderate quality).

Patients receiving antibiotics probably had lower risk of reccurence both within one month (six trials, [9,10,24,26,28] OR 0.48, 95% CI 0.30 to 0.77, I^2=45%; 63 fewer (86 fewer to 27 fewer) per 1000 patients; moderate quality; fig 2 and table 2), and at extended follow-up, from one to three months (two trials, [10,24] OR 0.64, 95% CI 0.48 to 0.85, I^2=0%; 78 fewer (118 fewer to 31 fewer) per 1000 patients; moderate quality; figure 2 and table 2). A subgroup by individual antibiotics (TMP-SMX versus clindamycin) suggested that there was no difference between clindamycin and TMP-SMX (interaction P = 0.71, figures 6).

Hospitalization was probably less common in patients randomised to antibiotics (two trials,[10,24] OR 0.55, 95% CI 0.32 to 0.94, I^2=0%; 17 fewer (26 fewer to 2 fewer) per 1000 patients; moderate quality; table 2).

Only one RCT (n=1057)[10] reported pain, additional surgical procedures, infection in a household member, invasive infections (table 2). Antibiotics probably reduced pain at 3 or 4 days (OR 0.76, 95% CI 0.60 to 0.97; 68 fewer (126 fewer to 8 fewer) per 1000 patients; moderate

quality) and 8 to 10 days of follow up (OR 0.56, 95% CI 0.35 to 0.88; 42 fewer (63 fewer to 11 fewer) per 1000 patients; moderate quality), as well as additional surgical procedures at 49 to 63 days of follow-up (OR 0.58, 95% CI 0.39 to 0.87; 52 fewer (78 fewer to 16 fewer) per 1000 patients; moderate quality). The risk of infection in a household member was probably lower with antibiotics, but the confidence interval included no effect (OR 0.58, 95% CI 0.34 to 1.01; moderate quality). Antibiotics probably did not appear to lower the risk of invasive infections at 7 to 14 days (OR 1.02, 95% CI 0.14 to 7.24; moderate quality), at 42 and 56 days (OR 7.46, 95% CI 0.15 to 376.12; moderate quality).

The incidence and severity of adverse events is likely to differ between antibiotics, thus we analysed the safety outcomes separately for each antibiotic (clindamycin and TMP-SMX). Both TMP-SMX (four trials,[9,10,24,26] OR 1.28, 95% CI 1.04 to 1.58, I^2=0%; 21 more (3 more to 43 more) per 1000 patients; moderate quality) and clindamycin (one trial,[9] OR 2.29, 95% CI 1.35 to 3.88; 95 more (28 more to 187 more) per 1000 patients; moderate quality) were associated with increased risk of overall gastrointestinal side effects. Clindamycin increases the risk of diarrhoea (one trial,[9] OR 2.71, 95% CI 1.50 to 4.89; 96 more (30 more to 193 more) per 1000 patients; high quality), while TMP-SMX probably does not (three trials,[9,10,26] OR 0.92, 95% CI 0.70 to 1.22, I^2=0%; moderate quality) (table 3). Two large trials[9,10] (n=2051) monitored for *C. difficile* infection (CDI) with routine clinical monitoring: no CDI occurred in any treatment arm. TMP-SMX probably increases the risk of nausea (TMP-SMX OR 1.49, 95% CI 0.98 to 2.25, I^2=11%; moderate quality), while clindamycin may not (OR 0.96, 95% CI 0.31 to 3.02; moderate quality). TMP-SMX does not appear to have an important effect on the risk of sepsis (one trial,[10] OR 7.24, 95% CI 0.14 to 364.86; moderate quality) or death (two trials,[9,10] OR 0.98, 95% CI 0.06 to 15.68; no difference (4 fewer to 4 more) per 1000; high quality) because both outcomes were so rare. The risk of anaphylaxis is uncertain (TMP-SMX OR 2.32, 95% CI 0.67 to 8.06; clindamycin OR 2.17, 95% CI 0.62 to

7.58; low quality, table 3 and table C in appendix 2).

Subgroup analyses and sensitivity analyses

There was only enough information to conduct pre-specified subgroup analyses for the treatment failure and recurrence outcomes (see above). Sensitivity analyses using alternative pooling methods, effect measures, and statistical models did not result in a change in interpretation (tables A to D in appendix 3). The confidence intervals for abscess treatment failure, late recurrence, hospitalization, gastrointestinal side effects and nausea excluded no effect with the DL method but not the HKSJ method (tables E in appendix 3). For the results of the primary analysis suggested statistically significant treatment effect, sensitivity analyses using plausible assumptions about missing data were not robust to the worst plausible analysis (Table F in appendix 3).

The results and interpretation of the network meta-analysis did not change when we used weakly informative priors instead of than uninformative priors (data not shown).

Comparative effects of alternative antibiotics

Of the 14 trials, seven [9,28-30,32]included direct comparison between different types of antibiotics.

Comparative effects on treatment failure

There was sufficient information to conduct an NMA for treatment failure only. The NMA included 12 trials, with eight trials comparing antibiotics to no antibiotics and five trials that compared different antibiotics to each other (there was one three-arm RCT;[9] figure 7). We grouped cephalosporins into early (first and second) generation or late (third and fourth) generation cephalosporins. We excluded a single trial that compared azithromycin to early cephalosporin because there was only one event,[31] and another trial in which both antibiotics were early generation cephalosporins.[33]

Pairwise comparisons had I^2 values from 0% to 17.3% (figure 8). There was no incoherence between the direct and indirect evidence for any of the comparisons using the back-calculation (figure 8) or node-splitting approach (figure 9; table D in appendix 2). TMP-SMX and clindamycin both reduce treatment failure compared to no antibiotics (NMA OR 0.61, 95% CI 0.41 to 0.85; NMA OR 0.55, 95% CI 0.33 to 0.87, both moderate quality). There did not appear to be a difference between clindamycin and TMP-SMX (high quality; table 4-5). With moderate quality, TMP-SMX and clindamycin probably confer a lower treatment failure than early generation cephalosporins (TMP-SMX NMA OR 0.42, 95% CI 0.12 to 1.07; clindamycin NMA OR 0.39, 95% CI 0.11 to 1.02; tables 6-7) and for late generation cephalosporins.

Comparative effects of TMP-SMX versus clindamycin on other outcomes

A single trial [9] reported recurrence, diarrhoea, and nausea within one month. Use of TMP-SMX, compared clindamycin, was probably associated with higher risk of abscess recurrence (OR 2.14, 95% CI 1.11 to 4.12; 67 more (7 more to 163 more) per 100 patients; low quality), but lower risk of diarrhoea (OR 0.29, 95% CI 0.16 to 0.55; 109 fewer (132 fewer to 66 fewer) per 1000 patients, high quality). Nausea was rare (OR 1.90,

95% CI 0.69 to 5.21; 20 more (7 fewer to 86 more) per 1000 patients, moderate quality; table 5).

Comparison between early cephalosporins

One trial[33] compared two early cephalosporins (cefadroxil verus cephalexin); and there was only one event (RD -0.04, 95% CI -0.15 to 0.07).

Discussion

Findings and interpretations

We found moderate-to-high quality evidence that in patients with uncomplicated skin abscesses who treated with I&D, adjuvant antibiotic therapy lowers the risks of treatment failure, abscess recurrence, hospitalisation, additional surgical procedures, and pain during treatment; but increases the risk of overall gastrointestinal side effects (TMP-SMX and clindamycin) and diarrhoea (with clindamycin) . The evidence regarding the effects of antibiotics on other important outcomes events (e.g. death, invasive infections, and sepsis) is less certain, however these outcomes occurred very infrequently.

This evidence is most directly applicable to antibiotics with activity against MRSA (TMP-SMX and clindamycin), which appeared to be more effective at reducing the risk of treatment failure than antibiotics without activity against MRSA. Using standard criteria for evaluating the credibility of a subgroup effect,[34] the MRSA active versus cephalosporin subgroup was one of a small number of pre-specified hypotheses, has biologic plausibility, [35] a low p-value in the test of interaction, and the subgroup effect proved large. We were unable to examine if there was a

similar effect on other outcomes because the RCTs that included antibiotics without MRSA activity did not report those outcomes. We judged the observed subgroup effect of moderate-to-high credibility.

The NMA of alternative antibiotic regimens could only be conducted for treatment failure. We found high quality evidence that there is no important difference in treatment failure between TMP-SMX and clindamycin, which is consistent with an RCT of patients with MRSA SSTIs.[36] A single study found that TMP-SMX may confer a higher risk of abscess recurrence than clindamycin, which is consistent with a previous RCT of SSTIs[37]. However, indirect evidence from our review suggests that this finding may be spurious: that study was also the only one of four where TMP-SMX did not reduce the risk of abscess recurrence compared to placebo – it did in all of the other studies and in the pooled effect. Moreover, when compared to no antibiotics, clindamycin did not appear to reduce the risk of abscess recurrence more than TMP-SMX. We did find high quality evidence that TMP-SMX has a substantially lower risk of diarrhoea than clindamycin.

Strengths and limitations

Our study has several strengths. First, we systematically identified RCTs and rigorously collected and analysed the data. We conducted a small number of pre-specified subgroup analyses to explore treatment heterogeneity, and a number of sensitivity analyses to examine robustness of effect estimates. Our review assessed both the effects of antibiotics versus no antibiotics, and the relative merit of different antibiotics, including a network meta-analysis that addressed the latter issue. The GRADE approach informed our assessment of the quality of evidence both in the comparison of antibiotics versus no antibiotics and the comparisons between antibiotics.

The results are primarily limited by the available studies. Four of the RCTs were published more than 30 years ago and surgical treatments as well as antibiotic resistance patterns have changed. The results and interpretation did not change when these trials were excluded from the analyses. Although we planned a number of hypotheses for exploring potential heterogeneity across studies, sufficient data were available only for treatment failure, recurrence within 1 month and for three hypotheses (≥18 vs < 18 years old, antibiotics with vs without MRSA activity, TMP-SMX versus clindamycin). In addition, the definition of outcomes varied among included trials.

Clinicians should consider local rates of CA-MRSA resistance to clindamycin and TMP-SMX; antibiotics will be less effective in areas with a substantial risk of resistance. Most of included studies involved patients treated in an emergency department. Considering the characteristics of involved patients and medical conditions may differ between emergency department and GPs, antibiotics may confer an even smaller benefit in patients who present to their GP. This evidence does not apply to pustules and papules. Moreover, rare adverse events are unlikely to be observed in RCTs. Important but rare adverse events include anaphylaxis, C. difficile infection (especially with clindamycin[38]), and Stevens-Johnson syndrome or toxic epidermal necrolysis (especially with TMP-SMX[39]).

Comparison with other studies

Two systematic reviews and meta-analyses have assessed the effect of adjunctive antibiotics versus no antibiotics in the treatment of skin abscess.[8,40] One systematic review[40] included four trials of 589 patients failed to detect a benefit of antibiotics on clinical cure (OR 1.17, 95% CI

0.70 to 1.95) and recurrence (RD 10 more per 100, 95% CI 2 fewer to 22 more). The other [8] included five RCTs and seven observational studies also failed to detect benefit with antibiotics on clinical cure rates (RR 1.03, 95% CI 0.97 to 1.08).

The difference in results is attributable to two recent large RCTs, with increased power to detect small-to-moderate effects. [9,10] Another reason that previous systematic reviews failed to show benefit is that the relative weight of trials comparing cephalosporins to placebo, which are likely do not confer a benefit, was greater.[35] The benefits of antibiotics are modest, and they come with an important risk of adverse effects. Some well described rare but serious adverse effects such as community-acquired *C. difficile* infection (especially with clindamycin), hypersensitivity (especially with TMP-SMX), and life-threatening skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome (especially with TMP-SMX) would not occur frequently enough to be detected with RCTs, but are important considerations nonetheless. It is therefore likely that some fully informed patients will choose antibiotics and others will decline.

Conclusions

Based on moderate to high quality evidence, antibiotics provide a modest reduction in the risk of treatment failure, recurrence, additional surgical procedures, and hospitalisation, and reduce pain during treatment. Antibiotics increase the risk of gastrointestinal side effects, such as nausea (TMP-SMX) and diarrhoea (clindamycin). This evidence is most applicable to TMP-SMX and clindamycin; cephalosporins are probably less or not effective. High quality evidence demonstrated that TMP-SMX and clindamycin have similar effects on treatment failure, but clindamycin has a substantially higher risk of diarrhoea. The decision whether or not to use antibiotics should take into account local MRSA resistance patterns,

individual patient clinical factors (e.g. severity of infection, immunocompromised state), and individual values and preferences (e.g. a strong desire to avoid diarrhoea).

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Contributors: WW, WWC, YML and RACS contributed equally to this work. RACS, GHG, XS, and WW conceived the study. XS and WW had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. WW, RC and RAS designed the search strategy. WW, WWC, YML and LL screened abstracts and full texts, and acquired the data and judged risk of bias in the studies. WW, RAS and JPDM performed the data analysis. WW, WWC and YML wrote the first draft of the manuscript. RACS, LL, XS, JPDM, GHG critically revised the manuscript. All authors have approved the manuscript.

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Competing interests*:* All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the

submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing statement: No additional data available

Transparency declaration*:* The lead author (XS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Figures legends

Figure 1. Flow chart of selection of studies

Figure 2. Effects of antibiotics versus no antibiotics on treatment failure and recurrence

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Figure 4. Subgroup analysis of treatment failure by type of antibiotics (TMP-SMX versus clindamycin)

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Table 1 Characteristics of included randomised controlled trials

Author (year)	No. of sites	No. of patients randomised	Study setting	Age	Male patients (No, %)	MSSA (No, %)	MRSA (No, %)	Surgical treatment	Intervention	Antibiotics dose and usage	Duration	Follow-up
RCTs comparing antibiotics versus placebo or standard care												
Daum 2017[9]	6	786	Emergency department	>6 months	140 (52.6)	140 (17.8) §	388(49.4) §	Incision and drainage	Clindamycin	300mg, tid‡	10d	40d
					152 (57.8)				TMP-SMX	160mg/800mg, bid‡	10d	
					156 (60.7)				Placebo		10d	
Duong 2010[24]	1	161	Emergency department	3 months to 18 years	28 (38.4)	7 (9.6)	58 (79.4)	Incision and draining	TMP-SMX	10-12mg/kg/d, divided into 2 dose	10d	90d
					34 (44.7)	6 (7.8)	61 (80.2)		Placebo	-	10d	
Llera 1985[25]	1	81	Emergency department	>16 years	18 (66.7)	NR	NR	Incision and drainage	Cephradine	250mg, qid	7d	7d
					9 (39.1)				Placebo	-	7d	
Macfie 1977a[28]	1	121	Emergency department	NR	NR	NR	NR	Incision, curettage and primary suture	Clindamycin	150mg q6h	4d	9d††
					NR	NR	NR		Usual care	-	-	
Macfie 1977b[28]	1	98	Emergency department	NR	NR	NR	NR	Incision and open drainage	Clindamycin	150mg q6h	4d	9d††
					NR	NR	NR		Usual care	-	-	
Rajendran	1	166	Integrated	NR	59 (72.0)	NR	87(87.8) †§	Surgically	Cephalexin	500 mg,qid	7d	7d

2007[27]			Soft Tissue Infection Services (ISIS) clinic		68 (81.0)	NR		drained	Placebo	-	7d	
Schmitz 2010[26]	4	212	Emergency department	>16 years	68 (0.7)	NR	50 (60.0)	Incision and drainage	TMP-SMX	320 mg/1600 mg, bid	7d	30d
					72 (0.6)		47 (47.0)		Placebo	-	7d	
Talan 2016[10]	5	1265	Emergency department	>12 years	364 (57.8)	100 (15.9)	274 (43.5)	Incision and drainage	TMP-SMX	160 mg/800 mg, bid	14d	63d
					362 (58.7)	102 (16.5)	291 (47.2)		Placebo	-	14d	
RCTs comparing alternative antibiotics*												
Bucko 2002a[29]	63	143	NR	>12 years	153 (52.6)[#]	NR	NR	NR	Cefditoren 200mg	200mg,bid	10d	24d
					141 (49.8)[#]				Cefditoren 400mg	400mg, bid	10d	
					133 (47.0)[#]				Cefuroxime 250mg	250mg, bid	10d	
Bucko 2002b[29]	69	104	NR	>12 years	140 (50.3)[#]	NR	NR	NR	Cefditoren 200mg	200mg,bid	10d	24d
					144 (52.0)[#]				Cefditoren 400mg	400mg, bid	10d	
					144 (52.7)[#]				Cefadroxil 250mg	250mg, bid	10d	
Giordano	39	102	Emergency	>13	102 (53.0)[#]	NR	NR	Incision and	Cefdinir	300mg, bid	10d	24d

2006[30]			department	years	104 (52.0) #			drainage	Cephalexin	250mg, qid	10d	
Keiichi 1982[33]	15	46	Dermatology department	No restriction	62 (72.1)#	NR	NR	NR	Cefadroxil	250mg,tid	14d	14d
					57 (64.8)	NR	NR		L-Cephalexin	500mg, bid	14d	
Miller 2015[32]	4	242	Emergency department	>6 months	135 (51.1)#	14 (11.0)	74 (58.3)	Incision and drainage	Clindamycin	300mg,tid‡	12d	40d
					139 (53.5)	16 (13.9)	72 (62.6)		TMP-SMX	320mg/1600mg, bid‡	12d	
Montero 1996[31]	4	14	NR	6 months to 2 years	49 (49.0)#	NR	NR	NR	Azithromycin	10mg/kg, qd	3d	14d
					57 (57.0)	NR	NR		Cefaclor	20mg/kg/d, divided into 3 dose	10d	

d=days; NR=not reported;

* These trials included the patient subgroup of skin abscess, and data were collected from the specific patient subgroup; # Data from trials involving patients with skin and soft tissue infection which did not report characteristics of patients with skin abscess; † The denominator was patients with a positive culture; †† Mean follow-up days; ‡ Dose for adult; § Characteristics of patients in both antibiotics and placebo group

Table 2 Summary of GRADE evidence profile of antibiotics vs placebo or standard care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No antibiotics	 Antibiotics	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Treatment failure 1 month	Odds ratio: 0.58 (95% CI 0.37 - 0.90) Based on data from 2517 patients in 8 studies Follow up 7 to 21 days	**93** per 1000	**56** per 1000 Difference: **37 fewer per 1000** (95% CI 56 fewer - 9 fewer)	**Low** Due to serious risk of bias and serious inconsistency [1]	Antibiotics probably reduce the risk of treatment failure
Treatment failure (antibiotics with activity against MRSA) *1 month*	Odds ratio: 0.45 (95% CI 0.33 - 0.62) Based on data from 2305 patients in 6 studies Follow up 7 to 21 days	**128** per 1000	**62** per 1000 Difference: **66 fewer per 1000** (95% CI 82 fewer - 45 fewer)	**High**	Antibiotics with activity against MRSA reduce the risk of treatment failure
Treatment failure (antibiotics without activity against MRSA) *1 month*	Odds ratio: 1.82 (95% CI 0.68 – 4.85) Based on data from 212 patients in 2 studies Follow up 7 to 21 days	**58** per 1000	**101** per 1000 Difference:**43 more per 1000** (95% CI 18 fewer – 172 more)	**Moderate** Due to serious imprecision [2]	Antibiotics without activity against MRSA may not reduce the risk of treatment failure
Recurrence within 1 month	Odds ratio: 0.48 (95% CI 0.30 - 0.77) Based on data from 2134 patients in 6 studies Follow up 7 to 30 days	**129** per 1000	**66** per 1000 Difference: **63 fewer per 1000** (95% CI 86 fewer - 27 fewer)	**Moderate** Due to serious risk of bias and borderline inconsistency [3]	Antibiotics probably reduce the risk of early abscess recurrence.
Late recurrence 1 to 3 months	Odds ratio: 0.64 (95% CI 0.48 - 0.85)	**267** per 1000	**189** per 1000	**Moderate** Due to serious risk of bias,	Antibiotics probably reduce the risk of late abscess recurrence.

	Based on data from 1111 patients in 2 studies Follow up 63 to 90 days	Difference: **78 fewer per 1000** (95% CI 118 fewer - 31 fewer)	borderline imprecision[4]	
Hospitalisation 3 months	Odds ratio: 0.55 (95% CI 0.32 - 0.94) Based on data from 1206 patients in 2 studies Follow up 40 to 90 days	**39** per 1000 **22** per 1000 Difference: **17 fewer per 1000** (95% CI 26 fewer - 2 fewer)	**Moderate** Due to serious imprecision[5]	Antibiotics probably reduce the risk of hospitalisation.
Pain (tenderness) (3 to 4 days)	Odds ratio: 0.76 (95% CI 0.60 – 0.97) Based on data from 1057 patients in 1 studies Follow up 3 to 4 days	**559** per 1000 **491** per 1000 Difference: **68 fewer per 1000** (95% CI 126 fewer - 8 fewer)	**Moderate** Due to serious imprecision[6]	Antibiotics probably increase the risk of pain at 3 to 4 days.
Pain (tenderness) (8 to 10 days)	Odds ratio: 0.56 (95% CI 0.35 – 0.88) Based on data from 1057 patients in 1 studies Follow up 8 to 10 days	**101** per 1000 **59** per 1000 Difference: **42 fewer per 1000** (95% CI 63 fewer - 11 fewer)	**Moderate** Due to serious imprecision[7]	Antibiotics may not increase the risk of pain at 8 to 10 days
Additional surgical procedures within 1 to 3 month	Odds ratio: 0.58 (95% CI 0.39 – 0.87) Based on data from 1013 patients in 1 studies Follow up 43 to 63 days	**136** per 1000 **84** per 1000 Difference: **52 fewer per 1000** (95% CI 78 fewer - 16 fewer)	**Moderate** Due to serious imprecision[8]	Antibiotics probably increase the risk of additional surgical procedures.
Infections in family members within 1 month	Odds ratio: 0.58 (95% CI 0.34 –1.01) Based on data from 1013 patients in 1 studies Follow up 7 to 14 days	**67** per 1000 **40** per 1000 Difference: **27 fewer per 1000** (95% CI 43 fewer - 1 more)	**Moderate** Due to serious imprecision[9]	Antibiotics probably do not increase the risk of infection in family members.

Invasive infections 1 month	Odds ratio: 1.02 (95% CI 0.14 – 7.24) Based on data from 1057 patients in 1 studies Follow up 7 to 14 days	**4** per 1000 **4** per 1000 Difference: **0 more per 1000** (95% CI 3 fewer - 24 more)	**Moderate** Due to serious imprecision[10]	Antibiotics probably do not reduce the risk of serious complications at 7 to 14 days.
Invasive infections 3 month	Odds ratio: 7.46 (95% CI 0.15 – 376.12) Based on data from 1013 patients in 1 studies Follow up 42 to 56 days	**0** per 1000 **1** per 1000 Difference: **2 more per 1000** (95% CI 4 fewer – 8 more)	**Moderate** Due to serious imprecision[11]	Antibiotics probably do not reduce the risk of serious complications at 42 to 56 days.

1. **Risk of bias: Serious.** There was substantial missing data/lost-to-follow-up: the results are not robust to worth plausible sensitivity analysis (assuming that missing patients from the control arms have the same rate of treatment failure as those with complete follow-up, and five times the rate of treatment failure in the patients who were lost to follow-up in the antibiotic arm); **Inconsistency: Serious.** Effects might differ in different type of antibiotics.
2. **Imprecision: Serious.** Confidence interval approaches no effect;
3. **Risk of bias: Serious.** There was substantial missing data/lost-to-follow-up: the results are not robust to worth plausible sensitivity analysis.; **Inconsistency: No serious.** The magnitude of statistical heterogeneity was high, with I^2: 45%, but the direction of effect was similar in almost all trials, favouring antibiotics over no antibiotics;
4. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up: results are not sensitive to worst plausible sensitivity analysis, OR 1.48 95%CI (0.55, 3.96); **Imprecision: No serious.** A single large study, and one small study contributed data to this outcome;
5. **Imprecision: Serious.** Confidence interval approaches no effect;
6. **Imprecision: Serious.** Only data from one study, confidence interval approaches no effect;
7. **Imprecision: Serious.** Only data from one study;
8. **Imprecision: Serious.** Data from one study only;
9. **Imprecision: Serious.** Only data from one study; confidence interval include no effect;
10. **Imprecision: Serious.** Only data from one study;
11. **Imprecision: Serious.** Only data from one study; confidence interval include no effect;

Evidence have summarized at Magic App (www.magicapp.org/public/guideline/jlRvQn)

Table 3 Summary of GRADE evidence profile of TMP-SMX/ Clindamycin vs no antibiotic

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No antibiotics Antibiotics	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
TMP-SMX vs no antibiotic				
Sepsis 1 month	Odds ratio: 7.24 (95% CI 0.14 - 364.86) Based on data from 1247 patients in 1 studies Follow up 49-63 days	**0** per 1000 **2** per 1000 Difference: **2 more per 1000** (95% CI 3 fewer - 6 more)	**Moderate** Due to serious imprecision[1]	Antibiotics probably do not decrease the risk of sepsis.
Death 3 months	Odds ratio: 0.98 (95% CI 0.06 - 15.68) Based on data from 1763 patients in 2 studies Follow up 30 to 90 days	**1** per 1000 **1** per 1000 Difference: **0 fewer per 1000** (95% CI 4 fewer - 4 more)	**High** Borderline imprecision	Antibiotics do not reduce the risk of death.
Gastrointestinal side effects While taking antibiotics	Odds ratio: 1.28 (95% CI 1.04 - 1.58) Based on data from 2124 patients in 4 studies Follow up 30 to 90 days	**85** per 1000 **106** per 1000 Difference: **21 more per 1000** (95% CI 3 more - 43 more)	**Moderate** Due to serious imprecision[2]	TMP-SMX probably increases the risk of gastrointestinal side effects.
Nausea While taking antibiotics	Odds ratio: 1.49 (95% CI 0.98 - 2.25) Based on data from 1975 patients in 3 studies	**24** per 1000 **35** per 1000 Difference: **11 more per 1000**	**Moderate** Due to serious imprecision[3]	TMP-SMX probably increases the risk of nausea.

	Follow up 30 to 63 days	(95% CI 0 fewer - 28 more)		
Diarrhoea 3 months	Odds ratio: 0.92 (95% CI 0.7 - 1.22) Based on data from 1912 patients in 3 studies Follow up 30 to 63 days	**67** per 1000 Difference: **5 fewer per 1000** (95% CI 19 fewer - 14 more)	**62** per 1000	**Moderate** Due to serious imprecision[4]	TMP-SMX probably does not increase the risk of diarrhoea.
Anaphylaxis Minutes to days	Odds ratio: 2.32 (95% CI 0.67 - 8.06) Based on data from 877 patients in 3 studies Follow up 30 to 90 days	**7** per 1000 Difference: **8 more per 1000** (95% CI 2 fewer - 44 more)	**15** per 1000	**Low** Due to serious risk of bias and imprecision[5]	Antibiotics probably not increase the risk of anaphylaxis.
Clindamycin vs no antibiotics					
Gastrointestinal side effects While taking antibiotics	Odds ratio: 2.29 (95% CI 1.35 - 3.88) Based on data from 520 patients in 1 studies Follow up 30 to 90 days	**90** per 1000 Difference: **95more per 1000** (95% CI 28 more - 187 more)	**185** per 1000	**High**	Clindamycin increases the risk of gastrointestinal side effects.
Nausea While taking antibiotics	Odds ratio: 0.96 (95% CI 0.31 - 3.02) Based on data from 520 patients in 1 studies Follow up 30 to 63 days	**24** per 1000 Difference: **1 fewer per 1000** (95% CI 16 fewer - 45 more)	**23** per 1000	**Moderate** Due to serious imprecision[6]	Clindamycin may not increase the risk of nausea.
Diarrhoea 3 months	Odds ratio: 2.71 (95% CI 1.5 - 4.89)	**67** per 1000	**162** per 1000	**High**	Clindamycin increases the risk of diarrhoea.

	Based on data from 520 patients in 1 studies Follow up 30 to 63 days	Difference: **96 more per 1000** (95% CI 30 more - 193 more)		
Anaphylaxis Minutes to days	Odds ratio: 2.17 (95% CI 0.62 – 7.58) Based on data from 520 patients in 1 studies Follow up 30 to 90 days	**12** per 1000 Difference: **14 more per 1000** (95% CI 5 fewer - 72 more)	**26** per 1000	**Low** Due to serious risk of bias and imprecision [1]

Antibiotics probably not increase the risk of anaphylaxis.

1. **Imprecision: Serious.** Due to serious imprecision;
2. **Imprecision: Serious.** Confidence interval approaches no effect.;
3. **Imprecision: Serious.** Confidence interval approaches no effect;
4. **Imprecision: Serious.** Confidence interval approaches no effect.;
5. **Risk of bias: Serious.** Selective outcome reporting: studies without any events are likely to have not reported this outcome, leading to overestimation of risk.; **Imprecision: Serious.** Few events. Not all studies reported anaphylaxis.;
6. **Imprecision: Very Serious.** Confidence interval approaches no effect.;
7. **Risk of bias: Serious.** Selective outcome reporting: studies without any events are likely to have not reported this outcome, leading to overestimation of risk; **Imprecision: Serious.** Few events. Not all studies reported anaphylaxis.;

Table 4. Risk difference per 1000 patients of various antibiotics from the network meta-analysis for treatment failure within 1 month

	No antibiotics	Early cephalosporin	Late cephalosporin	TMP-SMX	Clindamycin
No antibiotics	**No antibiotics**				
Early cephalosporin	51 (-34, 226)	**Early cephalosporin**			
Late cephalosporin	30 (-51, 244)	-20 (-109, 100)	**Late cephalosporin**		
TMP-SMX	-34 (-51, -12)	-85 (-260, 4)	-64 (-278, 24)	**TMP-SMX**	
Clindamycin	-39 (-58, -10)	-90 (-265, 1)	-69 (-283, 22)	-6 (-27, 21)	**Clindamycin**

Each number is a risk difference, per 1000 patients, and 95% credible interval. The rows are the reference category: a risk difference <0 favours the row. Green shading = high certainty; orange shading = moderate certainty; red shading = low certainty. Based on the median treatment failure rate in the no antibiotics arms, we assume that the baseline risk of treatment failure without antibiotics is 90 per 1000 patients.

Table 5 Summary of GRADE evidence profile of TMP-SMX vs Clindamycin

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Clindamycin	TMP/SMX	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Treatment failure 1 month	Odds ratio: 1.08 (95% CI 0.69 - 1.75) Based on data from 2673 patients in 7 studies Follow up 7 to 30 days	**109** per 1000	**119** per 1000 Difference: **10 more per 1000** (95% CI 53 fewer - 41 more)	**High** Borderline imprecision[1]	There is no important difference in treatment failure.
Recurrence within 1 month	Odds ratio: 2.14 (95% CI 1.11 - 4.12) Based on data from 436 patients in 1 studies Follow up 30 days	**68** per 1000	**135** per 1000 Difference: **67 more per 1000** (95% CI 7 more - 163 more)	**Low** Due to serious imprecision and serious inconsistency [2]	TMP/SMX probably results in higher risk of early abscess recurrence.
Diarrhoea 1 month	Odds ratio: 0.29 (95% CI 0.16 - 0.55) Based on data from 526 patients in 1 studies Follow up 30 days	**162** per 1000	**53** per 1000 Difference: **109 fewer per 1000** (95% CI 132 fewer - 66 fewer)	**High**[3]	TMP/SMX has a lower risk of diarrhoea.
Nausea 1 month	Odds ratio: 1.9 (95% CI 0.69 - 5.21)	**23** per 1000	**43** per 1000	**Moderate** Due to serious imprecision[4]	There is probably not an important difference in risk of nausea.

	Based on data from 526 patients in 1 studies Follow up 30 days	Difference: **20 more per 1000** (95% CI 7 fewer - 86 more)		

1. **Imprecision: No serious.** Borderline wide confidence intervals;
2. **Imprecision: Serious.** Data from one study only; confidence interval approaches no difference; **Inconsistency: Serious.** The results are not consistent with the subgroup analysis, nor with the indirect evidence.
3. **Imprecision: No serious.** Direct data from one study only. However, we did not rate down for imprecision because of high certainty indirect evidence from other conditions that clindamycin has a higher risk of diarrhoea than TMP/SMX;
4. **Imprecision: Serious.** Data from one study only; wide confidence intervals.

Table 6 Summary of GRADE evidence profile of TMP-SMX vs early cephalosporins

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cephalosporins TMP/SMX	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Treatment failure 1 month	Odds ratio: 0.42 (95% CI 0.12 - 1.07) Based on data from 1436 patients in 5 studies Follow up 7 to 21 days	**280** per 1000 **119** per 1000 Difference: **162 fewer per 1000** (95% CI 392 fewer - 7 more)	**Moderate** Due to serious imprecision[1]	TMP/SMX probably reduces the risk of treatment failure.

1. **Imprecision: Serious.** Confidence interval includes no difference.

Table 7 Summary of GRADE evidence profile of Clindamycin vs early cephalosporins

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cephalosporins Clindamycin	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Treatment failure 1 month	Odds ratio: 0.39 (95% CI 0.11 - 1.02) Based on data from 1572 patients in 5 studies Follow up 7 to 21 days	**280** per 1000 **109** per 1000 Difference: **171 fewer per 1000** (95% CI 401 fewer - 2 more)	**Moderate** Due to serious imprecision[1]	Clindamycin probably reduces the risk of treatment failure.

1. **Imprecision: Serious.** Confidence interval includes no difference.

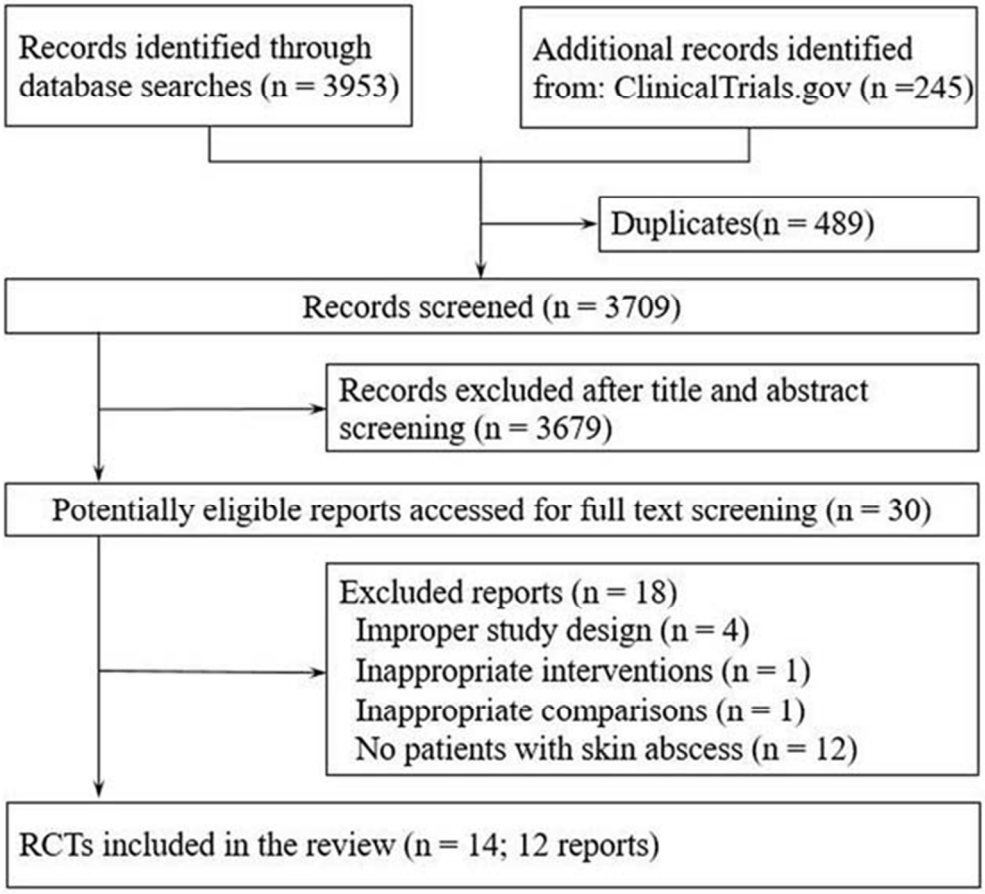

Fig 1 Flow chart of selection of studies

54x50mm (300 x 300 DPI)

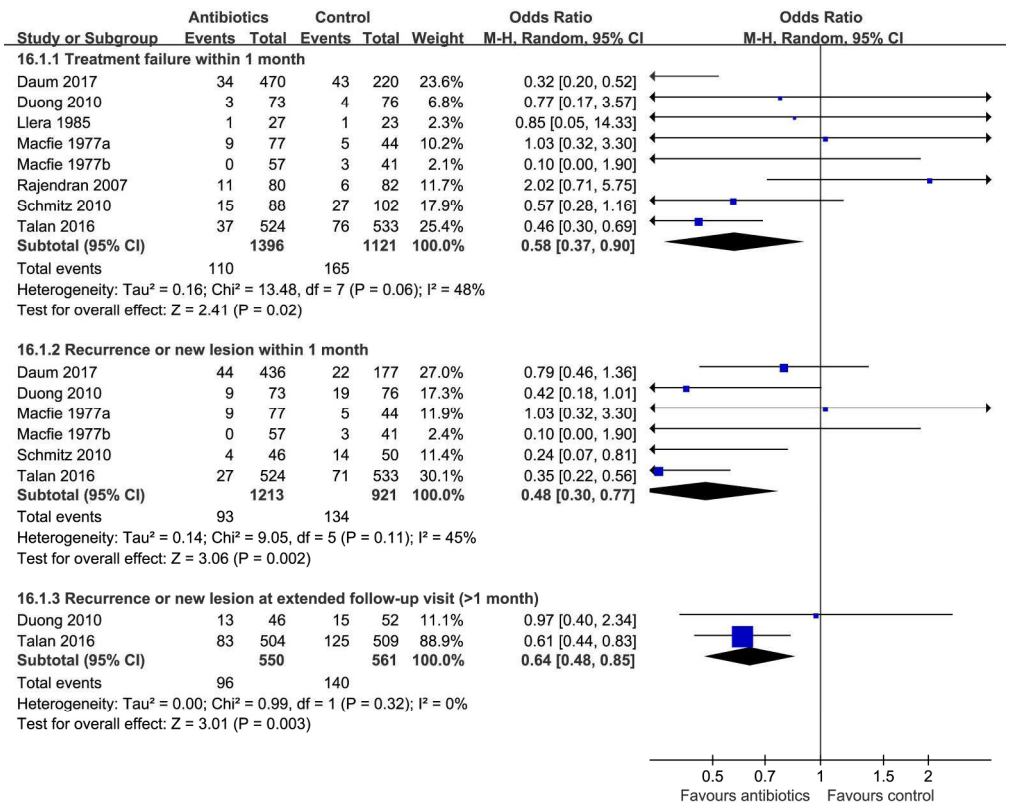

Fig 2 Effects of antibiotics versus no antibiotics on treatment failure and recurrence

195x158mm (300 x 300 DPI)

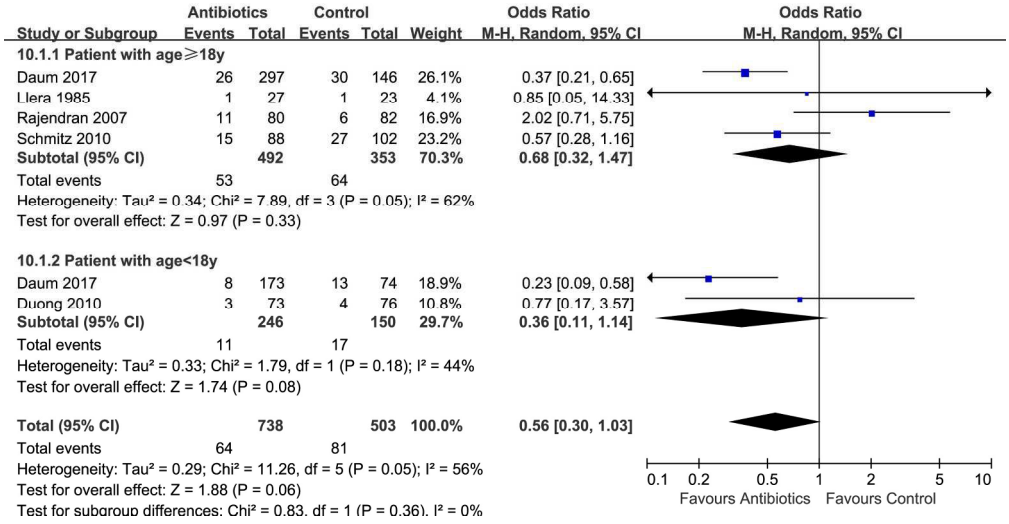

Fig 3 Subgroup analysis of treatment failure within one month by age (≥18 vs < 18 years old)

195x101mm (300 x 300 DPI)

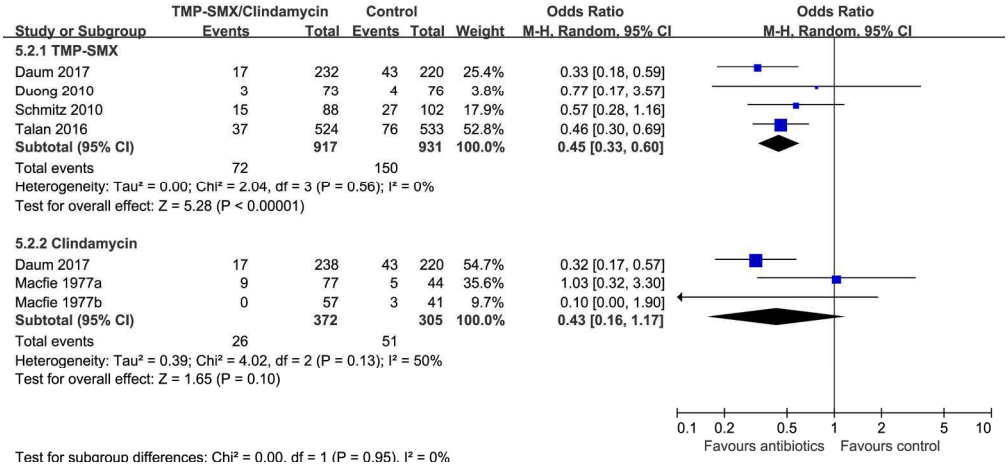

Fig 4 Subgroup analysis of treatment failure by type of antibiotics (TMP-SMX versus clindamycin)

195x90mm (300 x 300 DPI)

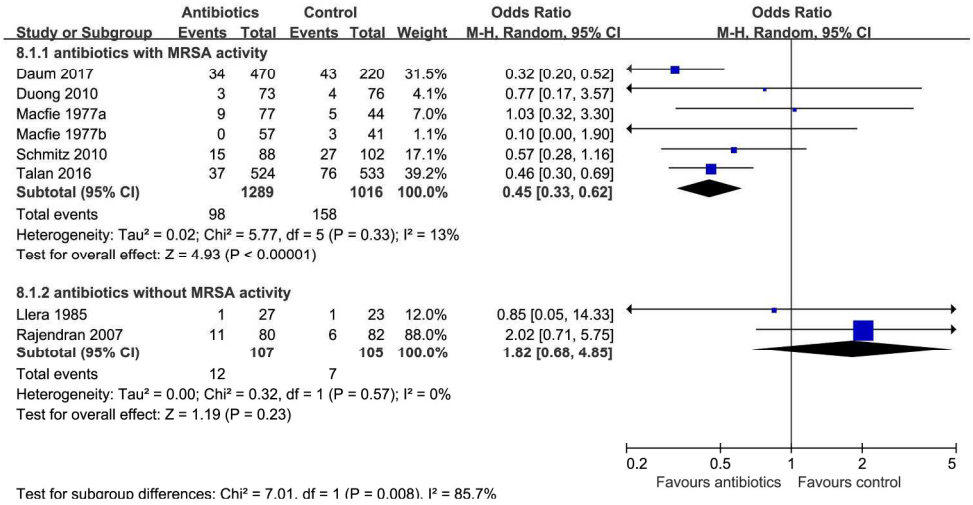

Fig 5 Subgroup analysis of treatment failure within 1 month by antibiotics with vs without MRSA activity

202x113mm (300 x 300 DPI)

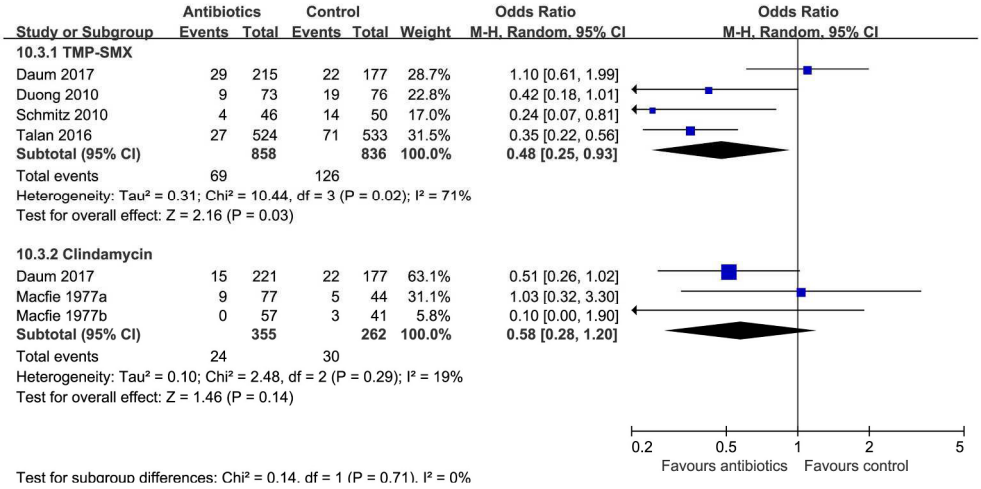

Fig 6 Subgroup analysis of recurrence by type of antibiotics (TMP-SMX versus clindamycin)

201x106mm (300 x 300 DPI)

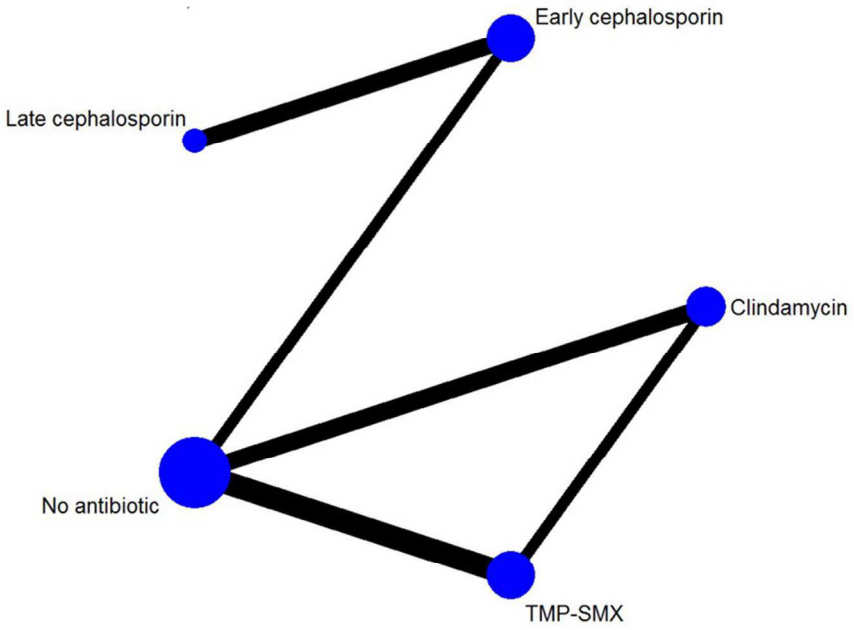

Fig 7 Network of included RCTs with available direct comparisons for treatment failure within 1 month.

80x59mm (300 x 300 DPI)

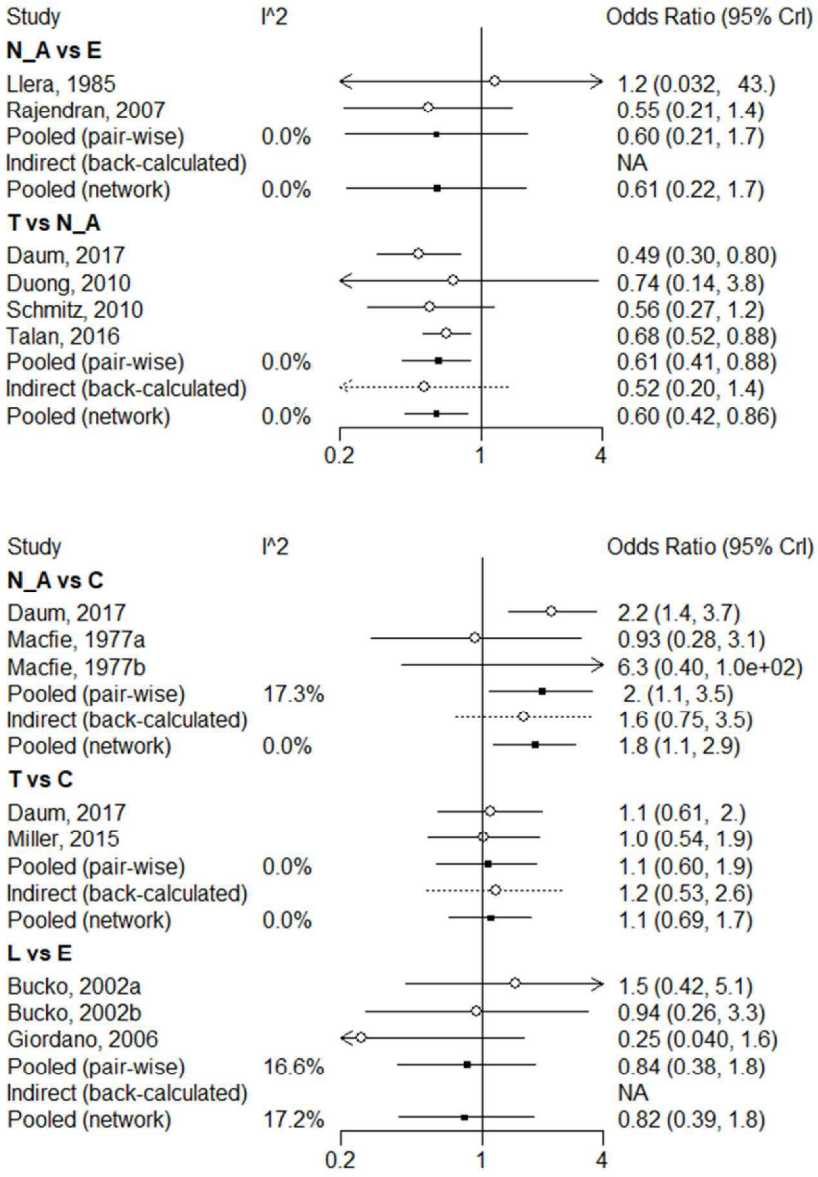

Fig 8 Forest plot of network meta-analysis results for treatment failure within 1 month.

244x343mm (300 x 300 DPI)

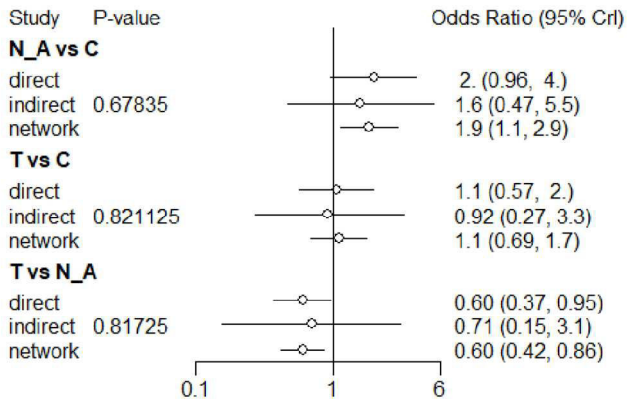

Fig 9 Assessment of network consistency, for all comparisons for which pairwise and indirect estimates were possible.

125x99mm (300 x 300 DPI)

Appendix 1 Search strategies

1. Medline (Ovid) (Search date: August 17, 2017)

1 exp abscess/
2 abscess* mp.
3 boil mp.
4 furunc* mp.
5 carbunc*mp.
6 1 or 2 or 3 or 4 or 5
7 exp skin diseases, infectious/
8 skin mp.
9 cutaneous mp.
10 superficial mp.
11 face mp.
12 facial mp.
13 7 or 8 or 9 or 10 or 11 or 12
14 6 and 13
15 exp anti-infective agents/
16 antibiotic* mp.
17 antimicrobial* mp.
18 antibacterial*.mp.
19 trimethoprim-sulfamethoxazole.mp.
20 clindamycin.mp.
21 cephalexin.mp.
22 cefazolin.mp.
23 doxycycline.mp.
24 minocycline.mp.
25 daptomycin.mp.
26 vancomycin.mp.
27 linezolid.mp.
28 nafcillin.mp.
29 dicloxacillin.mp.
30 televancin.mp.
31 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 clinical trial.mp.
33 clinical trial.pt.
34 random:.mp.
35 tu.xs.
36 33 or 34 or 35 or 36
37 14 and 32 and 37
38 limit 37 to humans

2. Embase (Ovid) (Search date: August 17, 2017)

1 exp skin abscess/

2 ((abscess* or boil or furunc* or carbunc*) adj6 (skin or cutaneous or superficial or face or facial)).mp.
3 1 or 2
4 exp antiinfective agent/
5 antibiotic*.mp.
6 antimicrobial*.mp.
7 antibacterial*.mp.
8 trimethoprim-sulfamethoxazole.mp.
9 clindamycin.mp.
10 cephalexin.mp.
11 cefazolin.mp.
12 doxycycline.mp.
13 minocycline.mp.
14 daptomycin.mp.
15 vancomycin.mp.
16 linezolid.mp.
17 nafcillin.mp.
18 dicloxacillin.mp.
19 televancin.mp.
20 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21 random:.mp.
22 clinical trial:.mp.
23 exp health care quality/
24 21 or 22 or 23
25 3 and 20 and 24

3. Cochrane Central Register of Controlled Trials (Ovid) (Search date: August 7, 2017)

1 exp abscess/
2 abscess*.mp.
3 boil.mp.
4 furunc*.mp.
5 carbunc*.mp.
6 1 or 2 or 3 or 4 or 5
7 exp skin diseases, infectious/
8 skin.mp.
9 cutaneous.mp
10 superficial.mp.
11 face.mp.
12 facial).mp.
13 7 or 8 or 9 or 10 or 11 or 12
14 6 and 13
15 exp Anti-Infective Agents/
16 antibiotic*.mp.
17 antimicrobial*.mp.

18 antibacterial*.mp.
19 trimethoprim-sulfamethoxazole.mp.
20 clindamycin.mp.
21 cephalexin.mp.
22 cefazolin.mp.
23 doxycycline.mp.
24 minocycline.mp.
25 daptomycin.mp.
26 vancomycin.mp.
27 linezolid.mp.
28 nafcillin.mp.
29 dicloxacillin.mp.
30 televancin.mp.
31 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

4. ClinicalTrials.gov (Search date: October 31, 2017)

skin infection OR abscess OR abscesses | Studies With Results

Appendix 2

Table A Inclusion criteria of abscess and definition of treatment failure/cure as reported in the included trials

Author (year)	Inclusion criteria of abscesses	Definition of treatment failure/cure
RCTs comparing antibiotics versus placebo or standard care		
Daum 2017[9]	A single abscess (defined as a circumscribed, drainable collection of pus) with a greatest diameter of 5.0 cm or less (≤3 cm for participants 6 to 11 months of age and ≤4 cm for participants 1 to 8 years of age), evidenced by two or more of the following signs or symptoms for at least 24 hours: erythema, swelling or induration, local warmth, purulent drainage, and tenderness to pain or palpation.	A lack of clinical cure was defined as lack of resolution of signs or symptoms of the infection, an inability to continue taking the study agent because of adverse effects within the first 48 hours, or any one of the following: recurrence at the original site of infection or occurrence of a skin infection at a new body site, unplanned surgical treatment of the skin infection, or hospitalization related to the infection.
Duong 2010[24]	Skin abscesses and were nontoxic, with temperature less than 38.4 °C, skin abscess included the presence of all of the following features: (1) acute onset within 1 week, (2) fluctuance,(3) erythema, (4) induration, and (5) tenderness, with or without purulent drainage.	Treatment failure was defined as the presence of any of the signs or symptoms (erythema, warmth, induration, fluctuance, tenderness, and drainage) at the 10-day follow-up or worsening signs or symptoms before the 10-day follow-up requiring further surgical drainage, change in medication, or hospital admission for intravenous antibiotics. New lesions within 5 cm of the original abscess site were also considered treatment failures. New lesions may consist of folliculitis, furuncles, carbuncles, or abscesses.
Llera 1985[25]	Localized collection of pus causing a fluctuant soft tissue swelling and surrounded by firm granulation tissue and erythema.	It considered treatment failure if any sign of fluctuance, drainage, induration, warmth, or tendemess was present at seven days.

Macfie 1977[28]	Acute superficial abscesses	A recurrence was recorded first, if a further collection of pus appeared at the same site as the original incision, and secondly, if signs of infection, discharge or inflammation reappeared or persisted and became worse following incision.
Rajendran 2007[27]	Diagnostic criteria for an abscess:(1) acute onset within 7 days prior to enrollment; (2) purulent drainage or purulent aspirate; (3) erythema, induration (≥2 cm in diameter), or tenderness; and (4) evidence of lobulated fluid at time of enrollment	Clinical cure: at the 1-week follow-up visit if there was resolution of the following signs and symptoms: purulent wound drainage, erythema, fluctuance, localized warmth, pain/tenderness, and edema/induration Treatment failure, defined as the presence of any of those above symptoms.
Schmitz 2010[26]	Uncomplicated skin abscesses requiring incision and drainage	Treatment failure defined as no improvement after 2 days, development of a new separate lesion or worsening infection (required evidence of an increased diameter of abscess or cellulitis, or the presence of fever or systemic response) within 7 days, leading to an intervention.
Talan 2016[10]	A fluctuant and/or indurated lesion, or findings of a fluid-filled cavity on soft tissue ultrasound evaluation that, when opened reveals purulent material, receiving I&D and having a minimum diameter (along any axis) of at least 2 cm (measured from the borders of induration, if a fluctuant lesion, or borders of the abscess cavity on ultrasound, if not fluctuant)	Clinical failure was defined as fever, an increase in the maximal dimension of erythema by >25% from baseline, or worsening of wound swelling and tenderness by the visit during the treatment period (day 3 or 4); fever, no decrease in the maximal dimension of erythema from baseline, or no decrease in swelling or tenderness by the visit at the end of the treatment period (day 8–10); and fever or more than minimal erythema, swelling, or tenderness by the test-of-cure visit (day 14–21).
RCTs comparing alternative antibiotics		
Bucko 2002[29]	Mild to moderate uncomplicated skin or skin structure infections, at least 2 of the following local signs and symptoms: pain, tenderness, swelling, erythema, associated warmth, purulent drainage/discharge, induration, and regional lymph node swelling or tenderness	Patients were considered clinical cures if their pretreatment signs and symptoms of infection had improved or resolved and they did not need additional antibiotic therapy for the treatment of the skin or skin structure infection clinical failures: at the post treatment visit if they experienced either persistent or worsening signs and symptoms or an improvement only after the patient received additional antimicrobial therapy for the infection.

Giordano 2006[30]	A mild to moderate uncomplicated skin or skin structure infections, which included, but was not limited to, cellulitis, erysipelas, impetigo, simple abscess, wound infection, furunculosis, and folliculitis	Patients were considered clinical failure if they experienced persistent or worsening signs and symptoms, had onset of new USSSI signs/symptoms at the baseline infection site following at least 72 h of antibiotic therapy, or needed additional antimicrobial therapy for the skin infection.
Keiichi 1982[33]	Suppurative skin and soft tissue infections	No details provided
Miller 2015[32]	Patients with uncomplicated skin infections who had two or more of the following signs or symptoms for 24 or more hours: erythema, swelling or induration, local warmth, purulent drainage, and tenderness to pain or palpation. Abscess was defined as a circumscribed, drainable collection of pus.	A lack of clinical cure was defined as a lack of resolution of signs or symptoms of infection, the occurrence of side effects that necessitated discontinuation of treatment with the study medication within the first 48 hours, or any one of the following before the test-of-cure visit: occurrence of a skin infection at a new body site, unplanned surgical treatment of the skin infection, or hospitalization related to the infection.
Montero 1996[31]	Acute skin and/or soft tissue infections	Treatment failure was defined as no change in, or worsening of, signs and symptoms of infection.

USSSI= uncomplicated skin or skin structure infections

Table B Risk of bias of included randomised controlled trials

Author	Adequate randomisation sequence generation	Adequate allocation concealment	Blinding of participants	Blinding of caregivers	Blinding of outcome assessors	Infrequent missing outcome data‡
Bucko 2002a[29]	**Probably yes** Randomised, double-blind*	**Probably yes** Randomised, double-blind†	**Probably yes** Double-blind (details not reported)	**Probably yes** Double-blind (details not reported)	**Probably yes** Double-blind (details not reported)	**Probably yes** There were 8.9% (26/291), 9.2% (26/283), 6.4% (18/283) patients with missing data for cure rate at TOC in three groups, respectively
Bucko 2002b[29]	**Probably yes** Randomised, double-blind	**Probably yes** Randomised, double-blind	**Probably yes** Double-blind (details not reported)	**Probably yes** Double-blind (details not reported)	**Probably yes** Double-blind (details not reported)	**Probably yes** There were 7.2% (20/278), 6.5%(18/277), 9.2%(25/273) patients with missing data for cure rate at TOC in three groups, respectively
Daum 2017[9]	**Definitely yes** Variable-block randomisation was performed by an independent statistics and data-coordinating center	**Definitely yes** Variable-block randomisation was performed by an independent statistics and data-coordinating center	**Definitely yes** Participants and all study staff were unaware	**Definitely yes** Participants and all study staff were unaware	**Definitely yes** Participants and all study staff were unaware	**Probably no** There were 10.5% (28/266), 11.8% (31/263), 14.3% (37/257) patients with missing data in three groups for cure rate at TOC, respectively; **Definitely no** There were 12.0% (32/266), 14.1% (37/263), 15.2% (39/257) patients with missing data for cure rate at 1 month in three groups, respectively

Duong 2010[24]	**Definitely yes** Computer randomisation	**Probably yes** Randomised, double-blind	**Definitely yes** The patient, parents, and clinician who assessed the clinical outcome were blinded to group assignment	**Definitely yes** The patient, parents, and clinician who assessed the clinical outcome were blinded to group assignment	**Definitely yes** The patient, parents, and clinician who assessed the clinical outcome were blinded to group assignment	**Probably yes** There were 9.6% (8/84) and 5.1% (4/77) patients in control and TMP groups with missing data for 10d treatment failure rate, respectively; **Definitely no** 37.3% (36/77) and 41.0% (32/84) patients in TMP and control groups with missing data for 30d new lesions, respectively
Giordano 2006[30]	**Definitely yes** Computer randomisation	**Probably yes** Details not reported, investigator-blinded	**Definitely no** Investigator-blinded	**Definitely yes** Investigator-blinded	**Probably yes** Investigator-blinded	**Probably no** There were 10.9% (21/192) and 13% (26/200) patients in Cefdinir and Cephalexin groups with missing data for cure rate at TOC, respectively
Keiichi 1982[33]	**Probably yes** Randomised, double-blind	**Probably yes** Randomised, double-blind	**Probably yes** Double-blind (details not reported)	**Probably yes** Double-blind (details not reported)	**Probably yes** Double-blind (details not reported)	**Definitely yes** Follow up rate was 100%
Llera 1985[25]	**Probably yes** Randomised, double-blind	**Probably yes** Randomised, double-blind	**Definitely yes** The patient, examining physician, or investigators were blinded to group assignment.	**Definitely yes** The patient, examining physician, or investigators were blinded to group assignment.	**Definitely yes** The patient, examining physician, or investigators were blinded to group assignment.	**Definitely no** There were (31/81) 38% with missing outcome data in two groups

Macfie 1977[28]	**Probably yes** Details not reported, open-label	**Probably no** Details not reported, open-label††	**Definitely no** Open-label	**Definitely no** Open-label	**Definitely no** Open-label	**Probably no** Details not reported
Miller 2015[32]	**Definitely yes** Variable-block randomisation was performed by an independent statistics and data-coordinating center	**Definitely yes** Performed by an independent contract research organization (EMMES) that developed the randomisation code	**Definitely yes** Participants and all study staff were unaware of the study-group assignments	**Definitely yes** Participants and all study staff were unaware of the study-group assignments	**Definitely yes** Participants and all study staff were unaware of the study-group assignments	**Probably no** There were 8.6% (7/127) and 11.3% (13/115) patients with abscess in Clindamycin and TMP-SMX groups with missing data for cure rate at TOC, respectively
Montero 1996[31]	**Probably yes** Details not reported, open-label	**Probably no** Open-label	**Definitely no** Open-label	**Definitely no** Open-label	**Definitely no** Open-label	**Definitely yes** There were 2% (2/100) and 2% (2/100) patients azithromycin and cefaclor groups with missing data for 10-14d treatment failure, respectively
Rajendran 2007[27]	**Definitely yes** A block randomisation scheme	**Probably yes** Sequentially numbered, sealed envelopes	**Definitely yes** All patients, investigators, and clinic staff were blinded to study group assignment	**Definitely yes** All patients, investigators, and clinic staff were blinded to study group assignment	**Definitely yes** All patients, investigators, and clinic staff were blinded to study group assignment	**Definitely yes** There were 2.4% (2/82) and 2.4% (2/84) patients in cephalexin and control groups with missing data for 7d treatment failure, respectively

Schmitz 2010[26]	**Definitely yes** A block randomisation scheme	**Definitely yes** Sealed envelopes	**Definitely yes** Patients and physicians were blinded to treatment	**Definitely yes** Patients and physicians were blinded to treatment	**Definitely yes** Patients and physicians were blinded to treatment	**Probably no** There were 8.3% (8/96) and 12.1% (14/116) patients in TMP/SMX and control groups with missing data for 7d treatment failure, respectively; **Definitely no** There were 52.1% (50/96) and 56.9% (66/116) patients in TMP/SMX and control groups with missing data for 30d new lesions, respectively
Talan 2016[10]	**Definitely yes** Web-based randomisation	**Definitely yes** Using double-blind, Web-based randomisation	**Definitely yes** The treatment arms masked to both the subject and the study staff	**Definitely yes** The treatment arms masked to both the subject and the study staff	**Definitely yes** The treatment arms masked to both the subject and the study staff	**Definitely no** There were 15.3% (96/629) and 16.7% (106/636) patients in placebo and TMP-SMX groups with missing data for cure rate at TOC, respectively

* Method for generating randomisation sequence not clearly reported. We judged that generating randomisation sequence was likely achieved regardless of blinding methods according to instructions. We followed this rule throughout the review.

† Method for allocation concealment not clearly reported. We judged that concealed allocation was likely achieved given it was a randomised double blinded trial, according to instructions. We followed this rule throughout the review.

†† Method for allocation concealment not clearly reported. We judged that concealed allocation was unlikely achieved given it was a randomised open label trial, according to instructions. We followed this rule throughout the review.

‡ We used the following rules to judge the infrequent missing outcome data for all included trials throughout the review: definitely yes: there were less than 5% patients with missing outcome data, and missing outcome data were generally balanced across treatment groups, with similar reasons for missing data across groups; probably yes: there were 5 to 10% patients with missing outcome data, and missing outcome data were generally balanced across treatment groups, with similar reasons for missing data across groups; probably no: there were 10% to 15% of missing outcome data; definitely no: there were over 15% patients with missing outcome data, or there were more than 5% absolute difference of missing outcome data between groups.

Table C Safety profile of antibiotics versus placebo or usual care

Outcomes	No. of trials	Events/total		OR(95%CI)	P value of test for overall	I^2	Tau^2	P value of interaction
		Antibiotics	Placebo or usual care					
Over all gastrointestinal side effects								
TMP-SMX vs Placebo	4	303/1064	252/1072	1.28(1.04, 1.58)	0.02	0%	0.00	0.05
Clindamycin vs Placebo	1	49/265	23/255	2.29(1.35, 3.88)	0.002	--	-	
Anaphylactic reaction*								
TMP-SMX vs Placebo	3	7/434	3/455	2.32(0.67,8.06)	0.19	28%	0.00	0.94
Clindamycin vs Placebo	1	7/265	3/255	2.17(0.62, 7.58)	0.22	--	-	
Nausea								
TMP-SMX vs Placebo	3	149/987	108/988	1.49(0.98,2.25)	0.06	11%	0.03	0.48
Clindamycin vs Placebo	1	6/265	6/255	0.96(0.31,3.02)	0.95	--	-	
Diarrhoea								
TMP-SMX vs Placebo	3	111/964	117/948	0.92(0.70,1.22)	0.56	0%	0.00	0.001
Clindamycin vs Placebo	1	43/265	17/255	2.71(1.50,4.89)	0.0009	--	-	
Sepsis*								
TMP-SMX vs Placebo	1	1/630	0/617	7.24(0.14,364.86)	0.32	-	-	

Death*								
TMP-SMX vs Placebo	2	1/891	1/872	0.98(0.06,15.68)	0.99	-	-	-
Clindamycin vs Placebo	1	0/265	0/255	-	-	-	-	

* Data were pooled using Peto's methods

Table D GRADE judgements for NMA of antibiotics for skin abscesses*

		Direct evidence								Indirect evidence									Network estimate			
Treatment 1	Treatment 2	Risk of bias	Inconsistency	Indirectness	Publication bias	Direct rating without imprecision	Direct is more precise (indirect imprecision		Direct rating with imprecision	Common comparator(s)	Treatment 1 vs first common comparator	Middle comparison	Treatment 2 vs final common comparator	Lowest of direct common comparisons Intransitivity		Indirect rating without imprecision		Indirect rating with imprecision	Higher rating of direct and indirect without Incoherence	Imprecision		Network rating final
No Abx	Early C	No	No	No	No	**High**	NA	-1	**Mod**										High	NA	-1	**Mod**
No Abx	Late C									Early C	High	NA	High	High	No	**High**	-2	**Low**	High	NA	-2	**Low**
No Abx	TMP/SMX	-1	No	No	No	**Mod**	Yes	No	**Mod**	Clinda.	High	NA	High	High	No	**High**	-2	**Low**	High	No	No	**Mod**
No Abx	Clinda.	-1	No	No	No	**Mod**	Yes	-1	**Mod**	TMP/SMX	High	NA	High	High	No	**High**	-2	**Low**	High	No	No	**Mod**
Early C	Late C	No	No	No	No	**High**	NA	-1	**Mod**										High	NA	-1	**Mod**
Early C	TMP/SMX									No Abx	High	NA	High	High	No	**High**	-1	**Mod**	High	NA	-1	**Mod**
Early C	Clinda.									No Abx	High	NA	High	High	No	**High**	-1	**Mod**	High	NA	-1	**Mod**
Late C	TMP/SMX									Early C/No Abx	High	High	High	High	No	**High**	-1	**Mod**	High	NA	-1	**Mod**
Late C	Clinda.									Early C/No Abx	High	High	High	High	No	**High**	-1	**Mod**	High	NA	-1	**Mod**
TMP/SMX	Clinda.	No	No	No	No	**High**	Yes	-1	**Mod**	No Abx	High	NA	High	Mod	No	**High**	-2	**Low**	High	No	No	**High**

No Abx, no antibiotics; Early C, early generation (1^{st}/2^{nd}) cephalosporins; later generation (3^{rd}/4^{th}) cephalosporins; TMP/SMX, trimethoprim/sulfamethoxazole; Clinda., clindamycin; Mod, Moderate; -1, rated down once because of serious concerns; -2, rated down twice because of very serious concern

*GRADE certainty ratings can be high, moderate, low, or very low. All comparisons started at high certainty and then were rated down if there were concerns with the GRADE domains listed. 'No' means that we judged there to not be any serious concerns with that domain for that comparison. '-1' means that we rated down the certainty by one category because of serious concerns and '-2= means that we rated down the certainty by two categories because of very serious concerns. For a detailed explanation of the GRADE domains and process for rating comparisons within a network meta-analysis, please see Puhan MA, et al. *BMJ.* 2014;349:g5630.

Appendix 3 Sensitivity analyses for the comparison between antibiotics versus placebo/standard care

Table A Sensitivity analyses using alternative effect measures

Outcomes	No. of trials	Events/total		RR(95%CI)	P value	I^2	Tau^2
		Antibiotics	Placebo/ standard care	M-H, Random			
Treatment failure within 1 month							
Antibiotics vs Placebo	8	110/1396	165/1121	0.62(0.42,0.91)	0.02	48%	0.12
Recurrence within 1 month							
Antibiotics vs Placebo	6	93/1213	134/921	0.53(0.35,0.80)	0.003	45%	0.11
Late recurrence 1 to 3 months							
Antibiotics vs Placebo	2	96/550	140/561	0.72(0.54,0.97)	0.03	18%	0.01
Hospitalization							
Antibiotics vs Placebo	2	19/597	35/609	0.56(0.33,0.96)	0.04	0%	0.00
Gastrointestinal side effects							
TMP-SMX vs Placebo	4	303/1064	252/1072	1.18(1.03,1.34)	0.02	0%	0.00
Clindamycin vs Placebo	1	49/265	23/255	2.05(1.29,3.26)	0.002	-	-
Nausea							

TMP-SMX vs Placebo	3	149/987	108/988	1.44(0.91,2.28)	0.12	19%	0.06
Clindamycin vs Placebo	1	6/265	6/255	0.96(0.31,2.94)	0.95	-	-
Diarrhoea							
TMP-SMX vs Placebo	3	111/964	117/948	0.93(0.73,1.19)	0.57	0%	0.00
Clindamycin vs Placebo	1	43/265	17/255	2.43(1.43,4.15)	0.001	-	-
Anaphylaxis							
TMP-SMX vs Placebo	3	7/434	3/455	1.78(0.49,6.42)	0.38	0%	0.00
Clindamycin vs Placebo	1	7/265	3/255	2.25(0.59,8.59)	0.24	-	-
Death							
TMP-SMX vs Placebo	2	1/891	1/872	0.98(0.06,15.62)	0.99	-	-
Clindamycin vs Placebo	1	0/265	0/255	-	-	-	-
Sepsis							
TMP-SMX vs Placebo	1	1/630	0/617	2.94(0.12,71.99)	0.51	-	-

Table B Sensitivity analyses using alternative statistical model

Outcomes	No. of trials	Events/total		OR(95%CI)	P value	I^2
		Antibiotics	Placebo/ standard care	M-H, Fixed		
Late reccurence						
Antibiotics vs Placebo	2	96/550	140/561	0.64(0.48.0.85)	0.003	0%
Hospitalization						
Antibiotics vs Placebo	2	19/597	35/609	0.54(0.31,0.96)	0.03	0%
Gastrointestinal side effects						
TMP-SMX vs Placebo	4	303/1064	252/1072	1.30(1.05,1.60)	0.01	0%
Clindamycin vs Placebo	1	49/265	23/255	2.29(1.35,3.88)	0.002	-
Nausea						
TMP-SMX vs Placebo	3	149/987	108/988	1.44(1.10,1.90)	0.008	11%
Clindamycin vs Placebo	1	6/265	6/255	0.96(0.31,3.32)	0.95	-
Diarrhoea						
TMP-SMX vs Placebo	3	111/964	117/948	0.92(0.70,1.22)	0.56	0%
Clindamycin vs Placebo	1	43/265	17/255	2.71(1.50,4.89)	0.0009	-

Anaphylaxis	3	14/699	3/455	2.41(0.80,7.22)	0.12	0%
TMP-SMX vs Placebo	3	7/434	3/455	2.10(0.63,6.96)	0.23	0%
Clindamycin vs Placebo	1	7/265	3/255	2.28(0.58,8.91)	0.24	-

Table C Sensitivity analyses using alternative pooling method

Outcomes	No. of trials	Events/total		OR(95%CI)	P value	I^2	Tau^2
		Antibiotics	Placebo/ standard care	M-H, Random			
Hospitalization							
Antibiotics vs Placebo	2	19/597	35/609	0.54(0.31,0.96)	0.04	0%	0.00
Infections in family members							
TMP-SMX vs Placebo	1	20/504	34/509	0.58(0.33,1.02)	0.06	-	-
Invasive infections (1 month)							
TMP-SMX vs Placebo	1	2/524	2/533	1.02(0.14,7.25)	0.99	-	-
Invasive infections (3 month)							
TMP-SMX vs Placebo	1	1/504	0/509	3.04(0.12,74.70)	0.50	-	-
Anaphylactic reaction							
TMP-SMX vs Placebo	3	7/434	3/455	1.80(0.49,6.58)	0.38	0%	0.00
Clindamycin vs Placebo	1	7/265	3/255	2.28(0.58, 8.91)	0.24	-	-
Sepsis							
TMP-SMX vs Placebo	1	1/630	0/617	2.94(0.12,72.38)	0.51	-	-

Death							
TMP-SMX vs Placebo	2	1/891	1/872	0.98(0.06,15.69)	0.99	-	-

Table D Sensitivity analyses using different inclusion criteria and different definition of treatment failure

Outcomes	No. of trials	Events/total		OR(95%CI)	P value	I^2	Tau^2
		Antibiotics	Placebo/ standard care	M-H, Random			
Sensitivity analyses by omiting trials exclusively reporting recurrence							
Treatment failure within 1 month	6	101/1262	157/1036	0.56 (0.35,0.90)	0.02	53%	0.16
Sensitivity analyses by omiting trials with patients treated by primary suture							
Treatment failure within 1 month	7	101/1319	160/1077	0.54 (0.34,0.86)	0.010	49%	0.16
Recurrence within 1 month	5	84/1136	129/877	0.43 (0.27,0.71)	0.0008	45%	0.13
Sensitivity analyses by omiting trials published before 1990							
Treatment failure within 1 month	5	100/1235	156/1013	0.56 (0.34,0.93)	0.03	62%	0.19
Recurrence within 1 month	4	84/1079	126/836	0.45 (0.27,0.74)	0.002	51%	0.13

Table E Sensitivity analyses using alternative methods of random effects meta-analysis

Outcomes	No. of trials	Events/total		OR (95%CI)	P value
		Antibiotics	Placebo/ standard care	HKSJ	
Treatment failure within 1 month					
Antibiotics vs Placebo	8	110/1396	165/1121	0.58 (0.33,1.01)	0.05
Recurrence within 1 month					
Antibiotics vs Placebo	6	93/1213	134/921	0.48 (0.26,0.88)	0.03
Late recurrence 1 to 3 month					
Antibiotics vs Placebo	2	96/550	140/561	0.64 (0.10,4.08)	0.20
Hospitalization					
Antibiotics vs Placebo	2	19/597	35/609	0.54 (0.19,1.56)	0.09
Gastrointestinal side effects					
TMP-SMX vs Placebo	4	303/1064	252/1072	1.28 (0.92,1.78)	0.10
Nausea					
TMP-SMX vs Placebo	3	149/987	108/988	1.49 (0.58,3.82)	0.21
Diarrhoea					
TMP-SMX vs Placebo	3	111/964	117/948	0.92 (0.74,1.15)	0.25

Anaphylaxis					
TMP-SMX vs Placebo	3	7/434	3/455	1.80(0.13,24.56)	0.44

HKSJ=Hartung-Knapp-Sidik-Jonkman

Table F Sensitivity analyses using different assumptions about missing data

Assumptions	No. of trials	Events/total		OR(95%CI)	P value	I^2	Tau^2
		Antibiotics	Placebo/ standard care				
Treatment failure within 1 month							
None has event*	8	110/1597	165/1293	0.59 (0.38,0.91)	0.02	46%	0.15
All had event†	8	311/1597	337/1293	0.71 (0.51,0.97)	0.03	46%	0.08
Best case scenario††	8	110/1597	337/1293	0.28 (0.15,0.53)	<0.0001	78%	0.52
Worst case scenario‡	8	311/1597	165/1293	1.59 (0.97,2.60)	0.07	68%	0.26
Worst plausible analysis #	8	183/1597	191/1293	0.82 (0.56,1.19)	0.30	44%	0.29
Recurrence within 1 month							
None has event*	6	93/1472	134/1171	0.52 (0.30,0.89)	0.02	57%	0.22
All had event†	6	352/1472	384/1171	0.62 (0.48,0.79)	0.0002	27%	0.02
Best case scenario††	6	93/1472	384/1171	0.15 (0.07,0.31)	<0.00001	82%	0.58
Worst case scenario‡	6	352/1472	134/1171	2.02 (0.96,4.24)	0.06	86%	0.62
Worst plausible analysis	6	193/1472	177/1171	0.83 (0.53,1.29)	0.4	61%	0.16

Later recurrence 1 to 3 month							
Worst plausible analysis #	2	187/713	178/713	1.48 (0.55,3.96)	0.44	87%	0.45
Hospitalizations §							
Worst plausible analysis #	2	39/713	41/713	0.94 (0.60,1.47)	0.78	0%	0.00
Pain (tenderness) (3 to 4 days)							
Worst plausible analysis #	1	337/636	352/629	0.89 (0.71,1.11)	0.29	-	-
Pain (tenderness) (8 to 10 days)							
Worst plausible analysis #	1	63/636	64/629	0.97 (0.67,1.40)	0.87	-	-
Additional surgical procedures							
Worst plausible analysis #	1	97/636	85/629	1.15 (0.84,1.58)	0.38	-	-

* All the participants lost to follow up did not have the event;

†All the participants lost to follow up had the event;

†† None of those lost to follow-up in the treatment group had the event and all those lost to follow-up in the control group did;

‡ All participants lost to follow-up in the treatment group had the event and none of those in the control group did;

Worst plausible analysis: Meta-analysis using the plausible most stringent $RI_{MPD/FU}$ (the incidence of outcome events in participants with missing data relative to those with complete follow-up). We defined a constant $RI_{MPD/FU}$ of 1.0 for control group missing participants, and 1.5, 2, 3, 5 for antibiotics group when the event rate was >40%, 30-40%, 10-30%, <10% respectively.

§ Pooled data using Peto's methods

		included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	*9*
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	8-9
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	9
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	*8-9*
RESULTS†			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	*14*
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	*14-15*
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	*12–15*
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	*12-15*
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	*14-15*
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	11
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	*13-14*
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	16-17

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	20

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Antibiotics for uncomplicated skin abscesses: systematic review and network meta-analysis

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Abstract

Objective

To assess the impact of adjunctive antibiotic therapy on uncomplicated skin abscesses.

Design

Systematic review and network meta-analysis.

Data sources

Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov.

Study selection

A BMJ Rapid Recommendation panel provided input on design, important outcomes and the interpretation of the results. Eligible RCTs included a comparison of antibiotics against no antibiotics or a comparison of different antibiotics in patients with uncomplicated skin abscesses, and reported outcomes pre-specified by the linked guideline panel.

Review methods

Reviewers independently screened abstracts and full texts for eligibility, assessed risk of bias and extracted data. We performed random-effects

meta-analyses that compared antibiotics to no antibiotics, along with a limited number of pre-specified subgroup hypotheses. We also performed network meta-analysis with a Bayesian framework to compare effects of different antibiotics. Quality of evidence was assessed with the GRADE approach.

Results

Fourteen RCTs including 4,198 patients proved eligible. Compared to no antibiotics, antibiotics probably lower the risk of treatment failure (odds ratio (OR) 0.58, 95% CI 0.37 to 0.90; low quality), recurrence within 1 month (0.48, 0.30 to 0.77; moderate quality), hospitalization (0.55, 0.32 to 0.94; moderate quality), and late recurrence (0.64, 0.48 to 0.85; moderate quality). However, relative to no use, antibiotics probably increase the risk of gastrointestinal side effects (TMP-SMX: 1.28, 1.04 to 1.58; moderate quality; clindamycin: 2.29, 1.35 to 3.88; high quality) and diarrhoea (clindamycin: 2.71, 1.50 to 4.89; high quality). Cephalosporins did not reduce the risk of treatment failure compared to placebo (moderate quality).

Conclusions

In patients with uncomplicated skin abscesses, moderate-to-high quality evidence suggests TMP-SMX or clindamycin confer a modest benefit for several important outcomes, but this is offset by a similar risk of adverse effects. Clindamycin has a substantially higher risk of diarrhoea than TMP-SMX. Cephalosporins are probably not effective.

Article summary

Strengths and limitations of this study

- This review is linked to a BMJ Rapid Recommendations project which aims to make rapid and trustworthy recommendations regarding new research that might change clinical practice.
- We systematically identified and rigorously collected the available evidence to inform choice of antibiotics for uncomplicated skin abscesses. We used the GRADE approach to assess the quality of evidence of estimates derived from pairwire and network meta-analysis.
- Sufficient data were available only for treatment failure and recurrence within 1 month, but not for other outcomes. In addition, limited data about rare adverse events were available in the RCTs.
- Most of included RCTs involved patients treated in an emergency department, limited evidence apply to patients who present to general practice.
- MRSA resistance patterns may differ across sites, individual patient clinical factors, values and preferences are variable as well. The decision whether or not to use antibiotics should take into account these importance factors.

Introduction

Skin and soft tissue infections (SSTIs) are common, accounting for approximately 5 physician visits per year for every 100 people, for which abscess/cellulitis is most common.[1] Hospital admissions for SSTIs appear to be increasingly common[2] possibly because of the high prevalence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA).[3] In the US, approximately 59% of patients with SSTIs were infected with CA-MRSA,[3,4] and CA-MRSA infections has become a global problem.

The appropriate strategies for managing SSTIs, especially those caused by CA-MRSA, are yet to be established. Until now, the role of adjuvant antibiotic therapy in addition to incision and drainage (I&D) has been controversial, [5-7] at least in part because randomised controlled trials (RCTs) have failed to consistently show benefit. A systematic review including five RCTs with 687 patients and seven observational studies with 1336 patients concluded that adjuvant antibiotics may not improve the chance of cure beyond the benefits of I&D alone.[8] Recently, two large RCTs were published, [9,10] both of which suggested that adjunctive trimethoprim and sulfamethoxazole (TMP-SMX) or clindamycin may improve cure rate compared to placebo.

Prompted by the BMJ Rapid Recommendation team's suggestions that this new evidence might change clinical practice, we conducted this systematic review to inform a BMJ Rapid Recommendation – a project that aims to make rapid and trustworthy recommendations regarding new research that might change clinical practice.[11] We addressed two clinical questions—in patients with uncomplicated skin abscesses, what is the impact of antibiotic plus I&D compared to I&D alone; and what are the impacts of the different antibiotic options

Methods

We followed the reporting standards set by Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [12] and the PRISMA network meta-analysis extension statement.[13]

Relationship to the BMJ Rapid Recommendation panel

According to the BMJ Rapid Recommendations process,[11] a semi-independent guideline panel provided critical oversight to the review and identified populations, subgroups, and outcomes of interest. The panel included three people with lived experience of skin abscesses, physicians (five general practitioners, two paediatricians, three infectious diseases specialists, a dermatologist and four general internists), and several research methodologists. The panel members helped interpret the evidence in this review and make clinical practice recommendations[14].

Patient involvement

Two adult patients and one parent of a child patient were full panel members of the linked BMJ Rapid Recommendation.[11] They worked with the rest of the panel, with the help of a patient liaison expert, to identify the outcomes that were important for decision-making; they also led the interpretation of the results based on what they expected the typical patient values and preferences to be, as well as the variation between patients.

Eligibility criteria

We included randomised controlled trials (RCTs) that included a comparison of antibiotics versus no antibiotics or a comparison of different types of antibiotics in children or adult patients with uncomplicated skin abscesses, and explicitly reported data on at least one of the outcomes pre-specified by the BMJ Rapid Recommendation guideline panel. Furuncles (boils) and carbuncles were included in the definition of skin abscesses, while pustules and papules were not. No restrictions were applied to types of antibiotics. The pre-specified outcomes included treatment failure, recurrence (at same or different site), hospitalisation, need for an additional surgical procedure, a similar infection in a household member, pain, invasive infections, gastrointestinal side effects, diarrhoea, nausea, death, and anaphylaxis.

Literature search

We searched Medline, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 17 August 2017 to identify relevant studies, without language restrictions. We combined database-specific subject headings (such as MeSH terms) and free-text terms regarding "skin abscess" and "anti-infective agents" to search for potentially eligible studies. We also searched ClinicalTrials.gov to identify any unpublished studies and reviewed the reference lists of the included RCTs. Supplementary Appendix 1 presents the full search strategy.

Study process

Three reviewers (WW, WWC and YML), independently and in duplicate, screened titles/abstracts for potential eligibility and full texts for final eligibility; assessed risk of bias; and collected data from each eligible trial using standardized, pilot tested forms. Reviewers resolved

disagreement through discussion or by adjudication by a third reviewer (LL).

Risk of bias assessment

We assessed risk of bias of RCTs using a modified version of the Cochrane tool, in which we used response options of "definitely or probably yes" (assigned a low risk of bias) and "definitely or probably no" (assigned a high risk of bias), an approach that has been validated.[15-17] The items for the risk of bias tool included random sequence generation; concealment of treatment allocation; blinding of participants, caregivers, and outcome assessors; infrequent missing outcome data.

Data extraction

We collected the following information from each eligible RCT: study characteristics (study design, total number of patients, length of follow up, whether the trial was an international study, number of sites, and stratification by skin abscess if a trial included other populations with infection); patient characteristics (gender, age and infection pathogen, type of abscess, and inclusion criterion); intervention characteristics (surgical treatment for abscess, type of antibiotics used in the treatment group, agents used in control, dose, and duration of treatment); and outcome data (outcomes of interest, events and numbers of patients included for analyses in each group).

Data analysis and rating quality of evidence

For our primary comparison of antibiotics vs. no antibiotics, we conducted pairwise meta-analyses. We used the random-effects

Mantel-Haenszel (M-H) method to estimate odds ratios (ORs) and 95% confidence intervals (CIs). For the outcomes with low event rate (<5%), we pooled data using Peto's method. We examined statistical heterogeneity among studies using the I^2 statistic and Cochran's chi-square test. We used complete case analysis for efficacy outcomes and as treated analysis for safety outcomes as our primary analyses.

We planned, according to the guideline panel's specification, five hypotheses to explain variability in effect estimates between studies: antibiotic MRSA coverage (hypothesizing larger effects with MRSA coverage versus no MRSA coverage), individual antibiotics (hypothesizing smaller effects with TMP-SMX versus clindamycin), type of patients (hypothesizing larger effects with children versus adults), treatment course (hypothesizing smaller effects with <7 days versus ≥7 days), and abscess size (hypothesizing larger effects with ≥5cm versus <5cm). We conducted subgroup analyses if there were at least two trials in each subgroup category.

We conducted the following sensitivity analyses to examine the robustness of effect estimates: analyses using alternative effect measures (odds ratio versus relative risk), statistical models (fixed versus random effects), pooling methods (Peto versus M-H), alternative methods for random effects meta-analysis (DerSimonian and Laird [DL] versus Hartung-Knapp-Sidik-Jonkman [HKSJ]), and alternative assumptions about missing data; as well as analyses omiting trials published before 1990 and trials with patients treated by primary suture rather than open drainage and, for treatment failure, excluding trials that considered recurrences as treatment failure.

We also conducted a network meta-analysis (NMA) of RCTs using a Bayesian approach to compare effects of alternative antibiotics. We fitted a

Bayesian random-effect hierarchical model with non-informative priors and adjusted for correlation between effects in multi-arm trials. We assumed common heterogeneity within the network. We generated posterior samples using Markov Chain Monte Carlo (MCMC) simulation technique running the analysis in three parallel chains. We used 10,000 burn-in simulations to allow convergence and then a further 100,000 simulations to produce the outputs. We assessed model convergence using Gelman and Rubin diagnostic test.[18] The primary network meta-analysis was conducted with uninformative priors with a uniform distribution, Unif(0, 5). We also conducted a sensitivity analysis with weakly informative priors (HN(0, 1)I(0,).

We report pooled ORs for direct, indirect and mixed network meta-analysis estimates and associated 95% credible intervals (CrI). We present the direct, indirect, and network effect estimates. We used the node-splitting approach for the assessment of loop inconsistency in our triangular loop.[19] Finally, we presented pooled risk differences (RD) for all the comparisons. To estimate absolute effect for treatment failure, we used the median baseline risk from the no antibiotics arms and applied it to the relative effect from the network estimates. We performed all analyses with R (R Core Team. 2016. Vienna, Austria: R Foundation for Statistical Computing) using the gemtc library.[20]

We followed the GRADE approach to rate the quality of evidence of estimates derived from pairwire and network meta-analysis.[21,22] Direct evidence from RCTs starts at high quality and can be rated down based on risk of bias, indirectness, imprecision, inconsistency, and publication bias. When the estimates were not robust to the worst plausible analysis, we rated down our certainty in the evidence for risk of bias.[23] For NMA estimates, we rated the quality of evidence in each of the direct, indirect, and NMA estimates.[22] The rating of indirect estimates starts at the

lowest rating of the two pairwise estimates that contribute as first order loops to the indirect estimate but can be rated down further for intransitivity. If direct and indirect estimates contributed similar power to the network estimate, then we used the higher rating. The network estimates were further rated down if they were incoherent.

Results

Our search yielded 4,198 potentially relevant reports and 12[9,10,24-33] ultimately proved eligible (figure 1). One report[29] included two independent RCTs, and the other[28] reported results of a factorial trial that also compared two surgical approaches and reported results separately for each approach. In total, there were 14 RCTs that enrolled a 3,541 patients with uncomplicated skin abscesses (range 1[9] to 1265), of which nine were multicenter studies,[9,10,26,29-33] and five were published prior to the year of 2000.[25,28,31,33] Eleven trails reported study setting, of which nine[9,10,24-26,28,30,32] (n = 3068) were conducted in emergency department, one[33] (n =174) in outpatient dermatology clinics, and the other one[27] in an Integrated Soft Tissue Infection Services (ISIS) clinic involving patients with high rates of comorbidity, such as infection with hepatitis C, hepatitis B, or HIV.

Two trials[25,26] exclusively enrolled adults, two exclusively enrolled children,[24,31] seven included both adults and children, [9,10,29,30,32,33]and three others provided no details.[27,28] Three trials reported abscess size of enrolled patients. [9,10,32] The largest trial[10] specifically focused on small abscesses, in which no patients had signs of systemic infection. Two trials[10,27] included a proportion of patients with diabetes (2.4% to 11%), and seven trials [9,24,25,26,29,32] excluded patients with diabetes. The most common pathogen cultured was MRSA, the proportion of which ranged from

43.5% to 87.8%. The resistance rates of clindamycin [9,24,32] ranged from 7.1% to 18%, while TMP-SMX [9,10,24,26,32] ranged from 0% to 2.6%. Ten trials reported surgical treatment for abscess, of which 9 performed incision and drainage [9,10,24-28,30,32] and the other performed incision, curettage, and primary suture[28] (table 1). The descriptions of abscess definitions were summarized in table A of appendix 2.

Antibiotics included TMP-SMX, clindamycin, early cephalosporins, late cephalosporins, and azithromycin. Eight trials [9,10,24-28] compared antibiotics (TMP-SMX, clindamycin, cephradine, cephalexin) to no antibiotics, of which six administered antibiotics for at least 7 days; [9,10,24-27] the two others used clindamycin for 4 days.[28] Six other trials [29-33] examined comparative effects of alternative antibiotics, and the treatment courses ranged from 3 days to 14 days. The length of follow-up ranged from 7 to 90 days across the trials (table 1).

All the 14 trials adequately generated their randomization sequence, 11 (78.6%) concealed treatment allocation, 10 (71.4%) blinded participants, 11 (78.6%) blinded caregivers, 11 (78.6%) blinded outcome assessors, and 6 (42.8%) trials had infrequent missing outcome. (table B in appendix 2).

Effects of antibiotics versus no antibiotics

Eight trials [9,10,24-28] compared antibiotics to no antibiotics. The risk of treatment failure was probably lower in patients randomised to antibiotics (eight trials,[9,10,24-28] OR 0.58, 95% CI 0.37 to 0.90, I^2=48%; risk difference 37 fewer (56 fewer to 9 fewer) per 1000 patients with uncomplicated skin abscess; low quality; figure 2 and table 2). For this outcome, we found sufficient information to conduct three pre-specified subgroup

analyses: analysis by age (≥18 versus < 18 years old) and individual antibiotics (TMP-SMX versus clindamycin) suggested no significant difference (interaction P = 0.36 and 0.95, figures 3 and 4). Antibiotics with activity against MRSA (TMP-SMX and clindamycin) proved more likely to reduce the risk of treatment failure than those without activity against MRSA (first generation cephalosporins) (interaction P=0.008; figure 5; antibiotics with MRSA activity, six trials, [9,10,24,26,28] OR 0.45, 95% CI 0.33 to 0.62 , I^2=13%; high quality; antibiotics without MRSA activity [cephalosporins], two trials,[25,27] OR 1.82, 95% CI 0.68 to 4.85, I^2= 0%; moderate quality).

Patients receiving antibiotics probably had lower risk of reccurence both within one month (six trials, [9,10,24,26,28] OR 0.48, 95% CI 0.30 to 0.77, I^2=45%; 63 fewer (86 fewer to 27 fewer) per 1000 patients; moderate quality; fig 2 and table 2), and at extended follow-up, from one to three months (two trials, [10,24] OR 0.64, 95% CI 0.48 to 0.85, I^2=0%; 78 fewer (118 fewer to 31 fewer) per 1000 patients; moderate quality; figure 2 and table 2). A subgroup by individual antibiotics (TMP-SMX versus clindamycin) suggested that there was no difference between clindamycin and TMP-SMX (interaction P = 0.71, figures 6).

Hospitalization was probably less common in patients randomised to antibiotics (two trials,[10,24] OR 0.55, 95% CI 0.32 to 0.94, I^2=0%; 17 fewer (26 fewer to 2 fewer) per 1000 patients; moderate quality; table 2).

Only one RCT (n=1057)[10] reported pain, additional surgical procedures, infection in a household member, invasive infections (table 2). Antibiotics probably reduced pain at 3 or 4 days (OR 0.76, 95% CI 0.60 to 0.97; 68 fewer (126 fewer to 8 fewer) per 1000 patients; moderate

quality) and 8 to 10 days of follow up (OR 0.56, 95% CI 0.35 to 0.88; 42 fewer (63 fewer to 11 fewer) per 1000 patients; moderate quality), as well as additional surgical procedures at 49 to 63 days of follow-up (OR 0.58, 95% CI 0.39 to 0.87; 52 fewer (78 fewer to 16 fewer) per 1000 patients; moderate quality). The risk of infection in a household member was probably lower with antibiotics, but the confidence interval included no effect (OR 0.58, 95% CI 0.34 to 1.01; moderate quality). Antibiotics probably did not appear to lower the risk of invasive infections at 7 to 14 days (OR 1.02, 95% CI 0.14 to 7.24; moderate quality), at 42 and 56 days (OR 7.46, 95% CI 0.15 to 376.12; moderate quality).

The incidence and severity of adverse events is likely to differ between antibiotics, thus we analysed the safety outcomes separately for each antibiotic (clindamycin and TMP-SMX). Both TMP-SMX (four trials,[9,10,24,26] OR 1.28, 95% CI 1.04 to 1.58, I^2=0%; 21 more (3 more to 43 more) per 1000 patients; moderate quality) and clindamycin (one trial,[9] OR 2.29, 95% CI 1.35 to 3.88; 95 more (28 more to 187 more) per 1000 patients; moderate quality) were associated with increased risk of overall gastrointestinal side effects. Clindamycin increases the risk of diarrhoea (one trial,[9] OR 2.71, 95% CI 1.50 to 4.89; 96 more (30 more to 193 more) per 1000 patients; high quality), while TMP-SMX probably does not (three trials,[9,10,26] OR 0.92, 95% CI 0.70 to 1.22, I^2=0%; moderate quality) (table 3). Two large trials[9,10] (n=2051) monitored for *C. difficile* infection (CDI) with routine clinical monitoring: no CDI occurred in any treatment arm. TMP-SMX probably increases the risk of nausea (TMP-SMX OR 1.49, 95% CI 0.98 to 2.25, I^2=11%; moderate quality), while clindamycin may not (OR 0.96, 95% CI 0.31 to 3.02; moderate quality). TMP-SMX does not appear to have an important effect on the risk of sepsis (one trial,[10] OR 7.24, 95% CI 0.14 to 364.86; moderate quality) or death (two trials,[9,10] OR 0.98, 95% CI 0.06 to 15.68; no difference (4 fewer to 4 more) per 1000; high quality) because both outcomes were so rare. The risk of anaphylaxis is uncertain (TMP-SMX OR 2.32, 95% CI 0.67 to 8.06; clindamycin OR 2.17, 95% CI 0.62 to

7.58; low quality, table 3 and table C in appendix 2).

Subgroup analyses and sensitivity analyses

There was only enough information to conduct pre-specified subgroup analyses for the treatment failure and recurrence outcomes (see above). Sensitivity analyses using alternative pooling methods, effect measures, and statistical models did not result in a change in interpretation (tables A to D in appendix 3). The confidence intervals for abscess treatment failure, late recurrence, hospitalization, gastrointestinal side effects and nausea excluded no effect with the DL method but not the HKSJ method (tables E in appendix 3). For the results of the primary analysis suggested statistically significant treatment effect, sensitivity analyses using plausible assumptions about missing data were not robust to the worst plausible analysis (Table F in appendix 3).

The results and interpretation of the network meta-analysis did not change when we used weakly informative priors instead of than uninformative priors (data not shown).

Comparative effects of alternative antibiotics

Of the 14 trials, seven [9,28-30,32]included direct comparison between different types of antibiotics.

Comparative effects on treatment failure

There was sufficient information to conduct an NMA for treatment failure only. The NMA included 12 trials, with eight trials comparing antibiotics to no antibiotics and five trials that compared different antibiotics to each other (there was one three-arm RCT;[9] figure 7). We grouped cephalosporins into early (first and second) generation or late (third and fourth) generation cephalosporins. We excluded a single trial that compared azithromycin to early cephalosporin because there was only one event,[31] and another trial in which both antibiotics were early generation cephalosporins.[33]

Pairwise comparisons had I^2 values from 0% to 17.3% (figure 8). There was no incoherence between the direct and indirect evidence for any of the comparisons using the back-calculation (figure 8) or node-splitting approach (figure 9; table A in appendix 4). TMP-SMX and clindamycin both reduce treatment failure compared to no antibiotics (NMA OR 0.61, 95% CI 0.41 to 0.85; NMA OR 0.55, 95% CI 0.33 to 0.87, both moderate quality). There did not appear to be a difference between clindamycin and TMP-SMX (high quality; table 4-5). With moderate quality, TMP-SMX and clindamycin probably confer a lower treatment failure than early generation cephalosporins (TMP-SMX NMA OR 0.42, 95% CI 0.12 to 1.07; clindamycin NMA OR 0.39, 95% CI 0.11 to 1.02; tables 6-7) and for late generation cephalosporins.

Comparative effects of TMP-SMX versus clindamycin on other outcomes

A single trial [9] reported recurrence, diarrhoea, and nausea within one month. Use of TMP-SMX, compared clindamycin, was probably associated with higher risk of abscess recurrence (OR 2.14, 95% CI 1.11 to 4.12; 67 more (7 more to 163 more) per 100 patients; low quality), but lower risk of diarrhoea (OR 0.29, 95% CI 0.16 to 0.55; 109 fewer (132 fewer to 66 fewer) per 1000 patients, high quality). Nausea was rare (OR 1.90,

95% CI 0.69 to 5.21; 20 more (7 fewer to 86 more) per 1000 patients, moderate quality; table 5).

Comparison between early cephalosporins

One trial[33] compared two early cephalosporins (cefadroxil verus cephalexin); and there was only one event (RD -0.04, 95% CI -0.15 to 0.07).

Discussion

Findings and interpretations

We found moderate-to-high quality evidence that in patients with uncomplicated skin abscesses who treated with I&D, adjuvant antibiotic therapy lowers the risks of treatment failure, abscess recurrence, hospitalisation, additional surgical procedures, and pain during treatment; but increases the risk of overall gastrointestinal side effects (TMP-SMX and clindamycin) and diarrhoea (with clindamycin) . The evidence regarding the effects of antibiotics on other important outcomes events (e.g. death, invasive infections, and sepsis) is less certain, however these outcomes occurred very infrequently.

This evidence is most directly applicable to antibiotics with activity against MRSA (TMP-SMX and clindamycin), which appeared to be more effective at reducing the risk of treatment failure than antibiotics without activity against MRSA. Using standard criteria for evaluating the credibility of a subgroup effect,[34] the MRSA active versus cephalosporin subgroup was one of a small number of pre-specified hypotheses, has biologic plausibility, [35] a low p-value in the test of interaction, and the subgroup effect proved large. We were unable to examine if there was a

similar effect on other outcomes because the RCTs that included antibiotics without MRSA activity did not report those outcomes. We judged the observed subgroup effect of moderate-to-high credibility.

The NMA of alternative antibiotic regimens could only be conducted for treatment failure. We found high quality evidence that there is no important difference in treatment failure between TMP-SMX and clindamycin, which is consistent with an RCT of patients with MRSA SSTIs.[36] A single study found that TMP-SMX may confer a higher risk of abscess recurrence than clindamycin, which is consistent with a previous RCT of SSTIs[37]. However, indirect evidence from our review suggests that this finding may be spurious: that study was also the only one of four where TMP-SMX did not reduce the risk of abscess recurrence compared to placebo – it did in all of the other studies and in the pooled effect. Moreover, when compared to no antibiotics, clindamycin did not appear to reduce the risk of abscess recurrence more than TMP-SMX. We did find high quality evidence that TMP-SMX has a substantially lower risk of diarrhoea than clindamycin.

Strengths and limitations

Our study has several strengths. First, we systematically identified RCTs and rigorously collected and analysed the data. We conducted a small number of pre-specified subgroup analyses to explore treatment heterogeneity, and a number of sensitivity analyses to examine robustness of effect estimates. Our review assessed both the effects of antibiotics versus no antibiotics, and the relative merit of different antibiotics, including a network meta-analysis that addressed the latter issue. The GRADE approach informed our assessment of the quality of evidence both in the comparison of antibiotics versus no antibiotics and the comparisons between antibiotics.

The results are primarily limited by the available studies. Four of the RCTs were published more than 30 years ago and surgical treatments as well as antibiotic resistance patterns have changed. The results and interpretation did not change when these trials were excluded from the analyses. Although we planned a number of hypotheses for exploring potential heterogeneity across studies, sufficient data were available only for treatment failure, recurrence within 1 month and for three hypotheses (≥18 vs < 18 years old, antibiotics with vs without MRSA activity, TMP-SMX versus clindamycin). In addition, the definition of outcomes varied among included trials.

Clinicians should consider local rates of CA-MRSA resistance to clindamycin and TMP-SMX; antibiotics will be less effective in areas with a substantial risk of resistance. Most of included studies involved patients treated in an emergency department. Considering the characteristics of involved patients and medical conditions may differ between emergency department and GPs, antibiotics may confer an even smaller benefit in patients who present to their GP. This evidence does not apply to pustules and papules. Moreover, rare adverse events are unlikely to be observed in RCTs. Important but rare adverse events include anaphylaxis, C. difficile infection (especially with clindamycin[38]), and Stevens-Johnson syndrome or toxic epidermal necrolysis (especially with TMP-SMX[39]). Only one trial[10] reported rate of serious invasive infection (0.2%-0.4%), however, the trial was under-powered to detect differences of this very rare but potentially fatal event.

Comparison with other studies

Two systematic reviews and meta-analyses have assessed the effect of adjunctive antibiotics versus no antibiotics in the treatment of skin

abscess.[8,40] One systematic review[40] included four trials of 589 patients failed to detect a benefit of antibiotics on clinical cure (OR 1.17, 95% CI 0.70 to 1.95) and recurrence (RD 10 more per 100, 95% CI 2 fewer to 22 more). The other [8] included five RCTs and seven observational studies also failed to detect benefit with antibiotics on clinical cure rates (RR 1.03, 95% CI 0.97 to 1.08).

The difference in results is attributable to two recent large RCTs, with increased power to detect small-to-moderate effects. [9,10] Another reason that previous systematic reviews failed to show benefit is that the relative weight of trials comparing cephalosporins to placebo, which are likely do not confer a benefit, was greater.[35] The benefits of antibiotics are modest, and they come with an important risk of adverse effects. Some well described rare but serious adverse effects such as community-acquired *C. difficile* infection (especially with clindamycin), hypersensitivity (especially with TMP-SMX), and life-threatening skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome (especially with TMP-SMX) would not occur frequently enough to be detected with RCTs, but are important considerations nonetheless. It is therefore likely that some fully informed patients will choose antibiotics and others will decline.

Conclusions

Based on moderate to high quality evidence, antibiotics provide a modest reduction in the risk of treatment failure, recurrence, additional surgical procedures, and hospitalisation, and reduce pain during treatment. Antibiotics increase the risk of gastrointestinal side effects, such as nausea (TMP-SMX) and diarrhoea (clindamycin). This evidence is most applicable to TMP-SMX and clindamycin; cephalosporins are probably less or not effective. High quality evidence demonstrated that TMP-SMX and clindamycin have similar effects on treatment failure, but clindamycin has

a substantially higher risk of diarrhoea. The decision whether or not to use antibiotics should take into account local MRSA resistance patterns, individual patient clinical factors (e.g. severity of infection, immunocompromised state), and individual values and preferences (e.g. a strong desire to avoid diarrhoea).

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Transparency declaration*:* The lead author (XS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Figures legends

Figure 1. Flow chart of selection of studies

Figure 2. Effects of antibiotics versus no antibiotics on treatment failure and recurrence

Figure 3. Subgroup analysis of treatment failure within one month by age (≥18 vs < 18 years old)

Figure 4. Subgroup analysis of treatment failure by type of antibiotics (TMP-SMX versus clindamycin)

Figure 5. Subgroup analysis of treatment failure within 1 month by antibiotics with vs without MRSA activity

Figure 6. Subgroup analysis of recurrence by type of antibiotics (TMP-SMX versus clindamycin)

Figure 7. Network of included RCTs with available direct comparisons for treatment failure within 1 month.

Figure 8. Forest plot of network meta-analysis results for treatment failure within 1 month.

Figure 9. Assessment of network consistency, for all comparisons for which pairwise and indirect estimates were possible.

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Table 1. Characteristics of included randomised controlled trials

Table 2. Summary of GRADE evidence profile of antibiotics vs placebo or standard care

Table 3. Summary of GRADE evidence profile of TMP-SMX/ Clindamycin vs no antibiotic

Table 4. Risk difference per 1000 patients of various antibiotics from the Network meta-analysis results for treatment failure within 1 month

Table 5. Summary of GRADE evidence profile of TMP-SMX vs Clindamycin

Table 6. Summary of GRADE evidence profile of TMP-SMX vs early cephalosporins

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Table 1 Characteristics of included randomised controlled trials

Author (year)	No. of sites	No. of patients randomised	Study setting	Age	Male patients (No, %)	MSSA (No, %)	MRSA (No, %)	Surgical treatment	Intervention	Antibiotics dose and usage	Duration	Follow-up
RCTs comparing antibiotics versus placebo or standard care												
Daum 2017[9]	6	786	Emergency department	>6 months	140 (52.6)	140 (17.8) §	388(49.4) §	Incision and drainage	Clindamycin	300mg, tid‡	10d	40d
					152 (57.8)				TMP-SMX	160mg/800mg, bid‡	10d	
					156 (60.7)				Placebo		10d	
Duong 2010[24]	1	161	Emergency department	3 months to 18 years	28 (38.4)	7 (9.6)	58 (79.4)	Incision and draining	TMP-SMX	10-12mg/kg/d, divided into 2 dose	10d	90d
					34 (44.7)	6 (7.8)	61 (80.2)		Placebo	-	10d	
Llera 1985[25]	1	81	Emergency department	>16 years	18 (66.7)	NR	NR	Incision and drainage	Cephradine	250mg, qid	7d	7d
					9 (39.1)				Placebo	-	7d	
Macfie 1977a[28]	1	121	Emergency department	NR	NR	NR	NR	Incision, curettage and primary suture	Clindamycin	150mg q6h	4d	9d††
					NR	NR	NR		Usual care	-	-	
Macfie 1977b[28]	1	98	Emergency department	NR	NR	NR	NR	Incision and open drainage	Clindamycin	150mg q6h	4d	9d††
					NR	NR	NR		Usual care	-	-	
Rajendran	1	166	Integrated	NR	59 (72.0)	NR	87(87.8) †§	Surgically	Cephalexin	500 mg,qid	7d	7d

2007[27]			Soft Tissue Infection Services (ISIS) clinic		68 (81.0)	NR		drained	Placebo	-	7d	
Schmitz 2010[26]	4	212	Emergency department	>16 years	68 (0.7)	NR	50 (60.0)	Incision and drainage	TMP-SMX	320 mg/1600 mg, bid	7d	30d
					72 (0.6)		47 (47.0)		Placebo	-	7d	
Talan 2016[10]	5	1265	Emergency department	>12 years	364 (57.8)	100 (15.9)	274 (43.5)	Incision and drainage	TMP-SMX	160 mg/800 mg, bid	14d	63d
					362 (58.7)	102 (16.5)	291 (47.2)		Placebo	-	14d	
RCTs comparing alternative antibiotics*												
Bucko 2002a[29]	63	143	NR	>12 years	153 (52.6)[#]	NR	NR	NR	Cefditoren 200mg	200mg,bid	10d	24d
					141 (49.8)[#]				Cefditoren 400mg	400mg, bid	10d	
					133 (47.0)[#]				Cefuroxime 250mg	250mg, bid	10d	
Bucko 2002b[29]	69	104	NR	>12 years	140 (50.3)[#]	NR	NR	NR	Cefditoren 200mg	200mg,bid	10d	24d
					144 (52.0)[#]				Cefditoren 400mg	400mg, bid	10d	
					144 (52.7)[#]				Cefadroxil 250mg	250mg, bid	10d	
Giordano	39	102	Emergency	>13	102 (53.0)[#]	NR	NR	Incision and	Cefdinir	300mg, bid	10d	24d

2006[30]			department	years	104 (52.0) #			drainage	Cephalexin	250mg, qid	10d	
Keiichi 1982[33]	15	46	Dermatology department	No restriction	62 (72.1)#	NR	NR	NR	Cefadroxil	250mg,tid	14d	14d
					57 (64.8)	NR	NR		L-Cephalexin	500mg, bid	14d	
Miller 2015[32]	4	242	Emergency department	>6 months	135 (51.1)#	14 (11.0)	74 (58.3)	Incision and drainage	Clindamycin	300mg,tid‡	12d	40d
					139 (53.5)	16 (13.9)	72 (62.6)		TMP-SMX	320mg/1600mg, bid‡	12d	
Montero 1996[31]	4	14	NR	6 months to 2 years	49 (49.0)#	NR	NR	NR	Azithromycin	10mg/kg, qd	3d	14d
					57 (57.0)	NR	NR		Cefaclor	20mg/kg/d, divided into 3 dose	10d	

d=days; NR=not reported;

* These trials included the patient subgroup of skin abscess, and data were collected from the specific patient subgroup; # Data from trials involving patients with skin and soft tissue infection which did not report characteristics of patients with skin abscess; † The denominator was patients with a positive culture; †† Mean follow-up days; ‡ Dose for adult; § Characteristics of patients in both antibiotics and placebo group

Table 2 Summary of GRADE evidence profile of antibiotics vs placebo or standard care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No antibiotics	 Antibiotics	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Treatment failure 1 month	Odds ratio: 0.58 (95% CI 0.37 - 0.90) Based on data from 2517 patients in 8 studies Follow up 7 to 21 days	**93** per 1000	**56** per 1000 Difference: **37 fewer per 1000** (95% CI 56 fewer - 9 fewer)	**Low** Due to serious risk of bias and serious inconsistency [1]	Antibiotics probably reduce the risk of treatment failure
Treatment failure (antibiotics with activity against MRSA) *1 month*	Odds ratio: 0.45 (95% CI 0.33 - 0.62) Based on data from 2305 patients in 6 studies Follow up 7 to 21 days	**128** per 1000	**62** per 1000 Difference: **66 fewer per 1000** (95% CI 82 fewer - 45 fewer)	**High**	Antibiotics with activity against MRSA reduce the risk of treatment failure
Treatment failure (antibiotics without activity against MRSA) *1 month*	Odds ratio: 1.82 (95% CI 0.68 – 4.85) Based on data from 212 patients in 2 studies Follow up 7 to 21 days	**58** per 1000	**101** per 1000 Difference:**43 more per 1000** (95% CI 18 fewer – 172 more)	**Moderate** Due to serious imprecision [2]	Antibiotics without activity against MRSA may not reduce the risk of treatment failure
Recurrence within 1 month	Odds ratio: 0.48 (95% CI 0.30 - 0.77) Based on data from 2134 patients in 6 studies Follow up 7 to 30 days	**129** per 1000	**66** per 1000 Difference: **63 fewer per 1000** (95% CI 86 fewer - 27 fewer)	**Moderate** Due to serious risk of bias and borderline inconsistency [3]	Antibiotics probably reduce the risk of early abscess recurrence.
Late recurrence 1 to 3 months	Odds ratio: 0.64 (95% CI 0.48 - 0.85)	**267** per 1000	**189** per 1000	**Moderate** Due to serious risk of bias,	Antibiotics probably reduce the risk of late abscess recurrence.

	Based on data from 1111 patients in 2 studies Follow up 63 to 90 days	Difference: **78 fewer per 1000** (95% CI 118 fewer - 31 fewer)	borderline imprecision[4]	
Hospitalisation 3 months	Odds ratio: 0.55 (95% CI 0.32 - 0.94) Based on data from 1206 patients in 2 studies Follow up 40 to 90 days	**39** per 1000 **22** per 1000 Difference: **17 fewer per 1000** (95% CI 26 fewer - 2 fewer)	**Moderate** Due to serious imprecision[5]	Antibiotics probably reduce the risk of hospitalisation.
Pain (tenderness) (3 to 4 days)	Odds ratio: 0.76 (95% CI 0.60 – 0.97) Based on data from 1057 patients in 1 studies Follow up 3 to 4 days	**559** per 1000 **491** per 1000 Difference: **68 fewer per 1000** (95% CI 126 fewer - 8 fewer)	**Moderate** Due to serious imprecision[6]	Antibiotics probably increase the risk of pain at 3 to 4 days.
Pain (tenderness) (8 to 10 days)	Odds ratio: 0.56 (95% CI 0.35 – 0.88) Based on data from 1057 patients in 1 studies Follow up 8 to 10 days	**101** per 1000 **59** per 1000 Difference: **42 fewer per 1000** (95% CI 63 fewer - 11 fewer)	**Moderate** Due to serious imprecision[7]	Antibiotics may not increase the risk of pain at 8 to 10 days
Additional surgical procedures within 1 to 3 month	Odds ratio: 0.58 (95% CI 0.39 – 0.87) Based on data from 1013 patients in 1 studies Follow up 43 to 63 days	**136** per 1000 **84** per 1000 Difference: **52 fewer per 1000** (95% CI 78 fewer - 16 fewer)	**Moderate** Due to serious imprecision[8]	Antibiotics probably increase the risk of additional surgical procedures.
Infections in family members within 1 month	Odds ratio: 0.58 (95% CI 0.34 –1.01) Based on data from 1013 patients in 1 studies Follow up 7 to 14 days	**67** per 1000 **40** per 1000 Difference: **27 fewer per 1000** (95% CI 43 fewer - 1 more)	**Moderate** Due to serious imprecision[9]	Antibiotics probably do not increase the risk of infection in family members.

Invasive infections 1 month	Odds ratio: 1.02 (95% CI 0.14 – 7.24) Based on data from 1057 patients in 1 studies Follow up 7 to 14 days	**4** per 1000 **4** per 1000 Difference: **0 more per 1000** (95% CI 3 fewer - 24 more)	**Moderate** Due to serious imprecision[10]	Antibiotics probably do not reduce the risk of serious complications at 7 to 14 days.
Invasive infections 3 month	Odds ratio: 7.46 (95% CI 0.15 – 376.12) Based on data from 1013 patients in 1 studies Follow up 42 to 56 days	**0** per 1000 **1** per 1000 Difference: **2 more per 1000** (95% CI 4 fewer – 8 more)	**Moderate** Due to serious imprecision[11]	Antibiotics probably do not reduce the risk of serious complications at 42 to 56 days.

1. **Risk of bias: Serious.** There was substantial missing data/lost-to-follow-up: the results are not robust to worth plausible sensitivity analysis (assuming that missing patients from the control arms have the same rate of treatment failure as those with complete follow-up, and five times the rate of treatment failure in the patients who were lost to follow-up in the antibiotic arm); **Inconsistency: Serious.** Effects might differ in different type of antibiotics.
2. **Imprecision: Serious.** Confidence interval approaches no effect;
3. **Risk of bias: Serious.** There was substantial missing data/lost-to-follow-up: the results are not robust to worth plausible sensitivity analysis.; **Inconsistency: No serious.** The magnitude of statistical heterogeneity was high, with I^2: 45%, but the direction of effect was similar in almost all trials, favouring antibiotics over no antibiotics;
4. **Risk of bias: Serious.** Incomplete data and/or large loss to follow up: results are not sensitive to worst plausible sensitivity analysis, OR 1.48 95%CI (0.55, 3.96); **Imprecision: No serious.** A single large study, and one small study contributed data to this outcome;
5. **Imprecision: Serious.** Confidence interval approaches no effect;
6. **Imprecision: Serious.** Only data from one study, confidence interval approaches no effect;
7. **Imprecision: Serious.** Only data from one study;
8. **Imprecision: Serious.** Data from one study only;
9. **Imprecision: Serious.** Only data from one study; confidence interval include no effect;
10. **Imprecision: Serious.** Only data from one study;
11. **Imprecision: Serious.** Only data from one study; confidence interval include no effect;

Evidence have summarized at Magic App (www.magicapp.org/public/guideline/jlRvQn)

Table 3 Summary of GRADE evidence profile of TMP-SMX/ Clindamycin vs no antibiotic

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No antibiotics Antibiotics	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
TMP-SMX vs no antibiotic				
Sepsis 1 month	Odds ratio: 7.24 (95% CI 0.14 - 364.86) Based on data from 1247 patients in 1 studies Follow up 49-63 days	**0** per 1000 **2** per 1000 Difference: **2 more per 1000** (95% CI 3 fewer - 6 more)	**Moderate** Due to serious imprecision[1]	Antibiotics probably do not decrease the risk of sepsis.
Death 3 months	Odds ratio: 0.98 (95% CI 0.06 - 15.68) Based on data from 1763 patients in 2 studies Follow up 30 to 90 days	**1** per 1000 **1** per 1000 Difference: **0 fewer per 1000** (95% CI 4 fewer - 4 more)	**High** Borderline imprecision	Antibiotics do not reduce the risk of death.
Gastrointestinal side effects While taking antibiotics	Odds ratio: 1.28 (95% CI 1.04 - 1.58) Based on data from 2124 patients in 4 studies Follow up 30 to 90 days	**85** per 1000 **106** per 1000 Difference: **21 more per 1000** (95% CI 3 more - 43 more)	**Moderate** Due to serious imprecision[2]	TMP-SMX probably increases the risk of gastrointestinal side effects.
Nausea While taking antibiotics	Odds ratio: 1.49 (95% CI 0.98 - 2.25) Based on data from 1975 patients in 3 studies	**24** per 1000 **35** per 1000 Difference: **11 more per 1000**	**Moderate** Due to serious imprecision[3]	TMP-SMX probably increases the risk of nausea.

	Follow up 30 to 63 days	(95% CI 0 fewer - 28 more)		
Diarrhoea 3 months	Odds ratio: 0.92 (95% CI 0.7 - 1.22) Based on data from 1912 patients in 3 studies Follow up 30 to 63 days	**67** per 1000 **62** per 1000 Difference: **5 fewer per 1000** (95% CI 19 fewer - 14 more)	**Moderate** Due to serious imprecision[4]	TMP-SMX probably does not increase the risk of diarrhoea.
Anaphylaxis Minutes to days	Odds ratio: 2.32 (95% CI 0.67 - 8.06) Based on data from 877 patients in 3 studies Follow up 30 to 90 days	**7** per 1000 **15** per 1000 Difference: **8 more per 1000** (95% CI 2 fewer - 44 more)	**Low** Due to serious risk of bias and imprecision[5]	Antibiotics probably not increase the risk of anaphylaxis.
Clindamycin vs no antibiotics				
Gastrointestinal side effects While taking antibiotics	Odds ratio: 2.29 (95% CI 1.35 - 3.88) Based on data from 520 patients in 1 studies Follow up 30 to 90 days	**90** per 1000 **185** per 1000 Difference: **95more per 1000** (95% CI 28 more - 187 more)	**High**	Clindamycin increases the risk of gastrointestinal side effects.
Nausea While taking antibiotics	Odds ratio: 0.96 (95% CI 0.31 - 3.02) Based on data from 520 patients in 1 studies Follow up 30 to 63 days	**24** per 1000 **23** per 1000 Difference: **1 fewer per 1000** (95% CI 16 fewer - 45 more)	**Moderate** Due to serious imprecision[6]	Clindamycin may not increase the risk of nausea.
Diarrhoea 3 months	Odds ratio: 2.71 (95% CI 1.5 - 4.89)	**67** per 1000 **162** per 1000	**High**	Clindamycin increases the risk of diarrhoea.

	Based on data from 520 patients in 1 studies Follow up 30 to 63 days	Difference: **96 more per 1000** (95% CI 30 more - 193 more)		
Anaphylaxis Minutes to days	Odds ratio: 2.17 (95% CI 0.62 – 7.58) Based on data from 520 patients in 1 studies Follow up 30 to 90 days	**12** per 1000 Difference: **14 more per 1000** (95% CI 5 fewer - 72 more)	**26** per 1000	**Low** Due to serious risk of bias and imprecision [1]

1. **Imprecision: Serious.** Due to serious imprecision;
2. **Imprecision: Serious.** Confidence interval approaches no effect.;
3. **Imprecision: Serious.** Confidence interval approaches no effect;
4. **Imprecision: Serious.** Confidence interval approaches no effect.;
5. **Risk of bias: Serious.** Selective outcome reporting: studies without any events are likely to have not reported this outcome, leading to overestimation of risk.; **Imprecision: Serious.** Few events. Not all studies reported anaphylaxis.;
6. **Imprecision: Very Serious.** Confidence interval approaches no effect.;
7. **Risk of bias: Serious.** Selective outcome reporting: studies without any events are likely to have not reported this outcome, leading to overestimation of risk; **Imprecision: Serious.** Few events. Not all studies reported anaphylaxis.;

Table 4. Risk difference per 1000 patients of various antibiotics from the network meta-analysis for treatment failure within 1 month

	No antibiotics	Early cephalosporin	Late cephalosporin	TMP-SMX	Clindamycin
No antibiotics	**No antibiotics**				
Early cephalosporin	51 (-34, 226)	**Early cephalosporin**			
Late cephalosporin	30 (-51, 244)	-20 (-109, 100)	**Late cephalosporin**		
TMP-SMX	-34 (-51, -12)	-85 (-260, 4)	-64 (-278, 24)	**TMP-SMX**	
Clindamycin	-39 (-58, -10)	-90 (-265, 1)	-69 (-283, 22)	-6 (-27, 21)	**Clindamycin**

Each number is a risk difference, per 1000 patients, and 95% credible interval. The rows are the reference category: a risk difference <0 favours the row. Green shading = high certainty; orange shading = moderate certainty; red shading = low certainty. Based on the median treatment failure rate in the no antibiotics arms, we assume that the baseline risk of treatment failure without antibiotics is 90 per 1000 patients.

Table 5 Summary of GRADE evidence profile of TMP-SMX vs Clindamycin

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Clindamycin	TMP/SMX	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Treatment failure 1 month	Odds ratio: 1.08 (95% CI 0.69 - 1.75) Based on data from 2673 patients in 7 studies Follow up 7 to 30 days	**109** per 1000	**119** per 1000 Difference: **10 more per 1000** (95% CI 53 fewer - 41 more)	**High** Borderline imprecision[1]	There is no important difference in treatment failure.
Recurrence within 1 month	Odds ratio: 2.14 (95% CI 1.11 - 4.12) Based on data from 436 patients in 1 studies Follow up 30 days	**68** per 1000	**135** per 1000 Difference: **67 more per 1000** (95% CI 7 more - 163 more)	**Low** Due to serious imprecision and serious inconsistency [2]	TMP/SMX probably results in higher risk of early abscess recurrence.
Diarrhoea 1 month	Odds ratio: 0.29 (95% CI 0.16 - 0.55) Based on data from 526 patients in 1 studies Follow up 30 days	**162** per 1000	**53** per 1000 Difference: **109 fewer per 1000** (95% CI 132 fewer - 66 fewer)	**High**[3]	TMP/SMX has a lower risk of diarrhoea.
Nausea 1 month	Odds ratio: 1.9 (95% CI 0.69 - 5.21)	**23** per 1000	**43** per 1000	**Moderate** Due to serious imprecision[4]	There is probably not an important difference in risk of nausea.

	Based on data from 526 patients in 1 studies Follow up 30 days	Difference: **20 more per 1000** (95% CI 7 fewer - 86 more)		

1. **Imprecision: No serious.** Borderline wide confidence intervals;
2. **Imprecision: Serious.** Data from one study only; confidence interval approaches no difference; **Inconsistency: Serious.** The results are not consistent with the subgroup analysis, nor with the indirect evidence.
3. **Imprecision: No serious.** Direct data from one study only. However, we did not rate down for imprecision because of high certainty indirect evidence from other conditions that clindamycin has a higher risk of diarrhoea than TMP/SMX;
4. **Imprecision: Serious.** Data from one study only; wide confidence intervals.

Table 6 Summary of GRADE evidence profile of TMP-SMX vs early cephalosporins

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cephalosporins TMP/SMX	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Treatment failure 1 month	Odds ratio: 0.42 (95% CI 0.12 - 1.07) Based on data from 1436 patients in 5 studies Follow up 7 to 21 days	**280** per 1000 **119** per 1000 Difference: **162 fewer per 1000** (95% CI 392 fewer - 7 more)	**Moderate** Due to serious imprecision[1]	TMP/SMX probably reduces the risk of treatment failure.

1. **Imprecision: Serious.** Confidence interval includes no difference.

Table 7 Summary of GRADE evidence profile of Clindamycin vs early cephalosporins

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Cephalosporins	 Clindamycin	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Treatment failure 1 month	Odds ratio: 0.39 (95% CI 0.11 - 1.02) Based on data from 1572 patients in 5 studies Follow up 7 to 21 days	**280** per 1000	**109** per 1000 Difference: **171 fewer per 1000** (95% CI 401 fewer - 2 more)	**Moderate** Due to serious imprecision[1]	Clindamycin probably reduces the risk of treatment failure.

1. **Imprecision: Serious.** Confidence interval includes no difference.

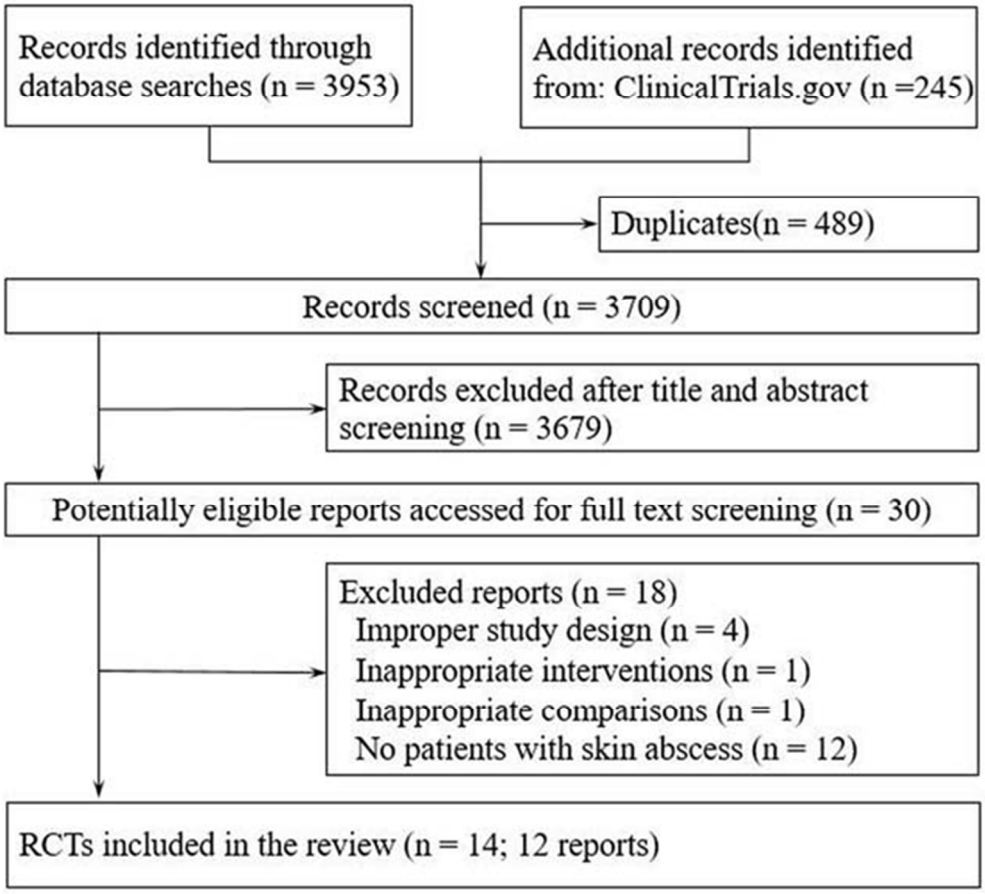

Fig 1 Flow chart of selection of studies

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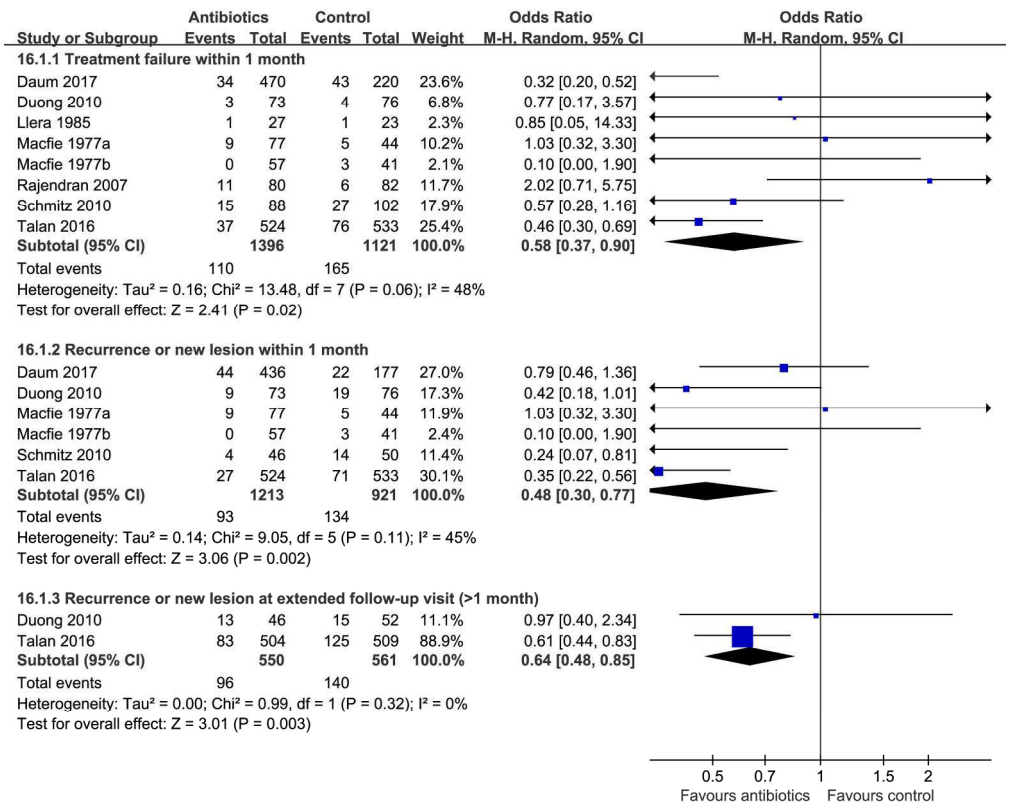

Fig 2 Effects of antibiotics versus no antibiotics on treatment failure and recurrence

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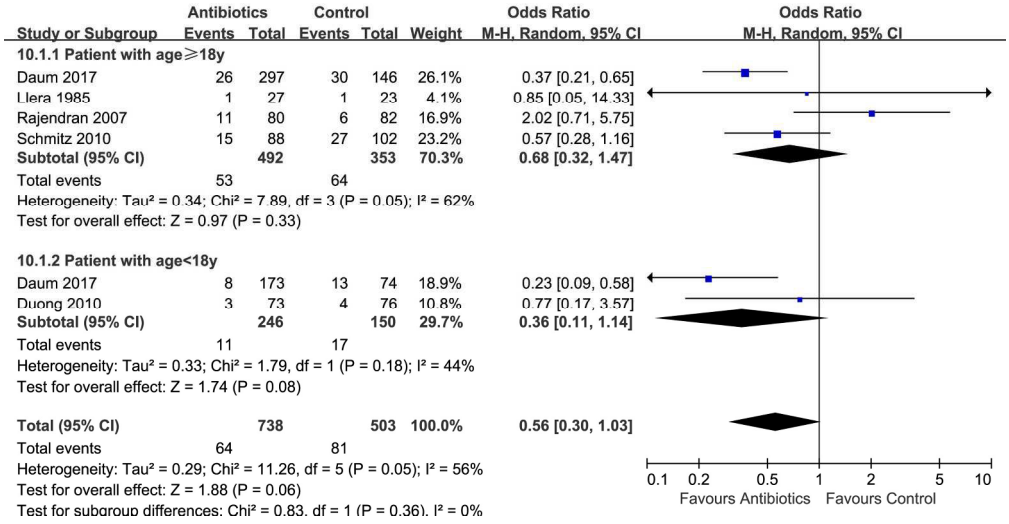

Fig 3 Subgroup analysis of treatment failure within one month by age (≥18 vs < 18 years old)

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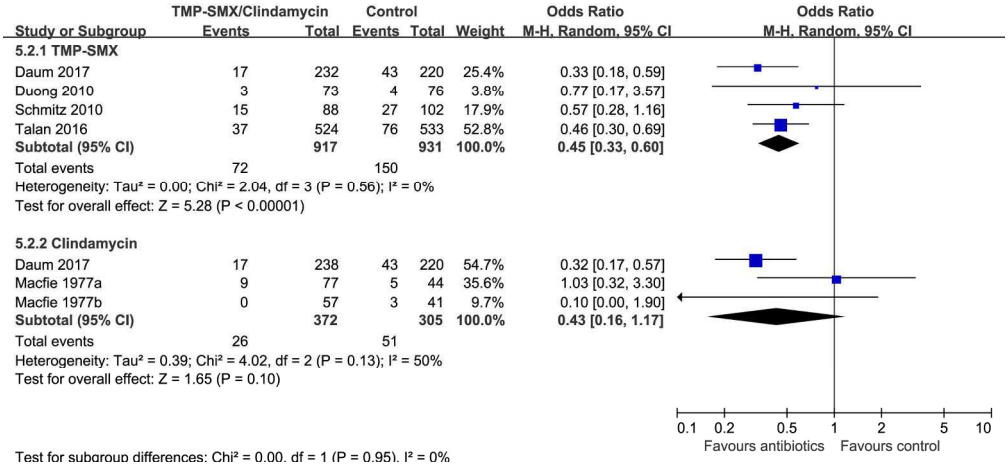

Fig 4 Subgroup analysis of treatment failure by type of antibiotics (TMP-SMX versus clindamycin)

195x90mm (300 x 300 DPI)

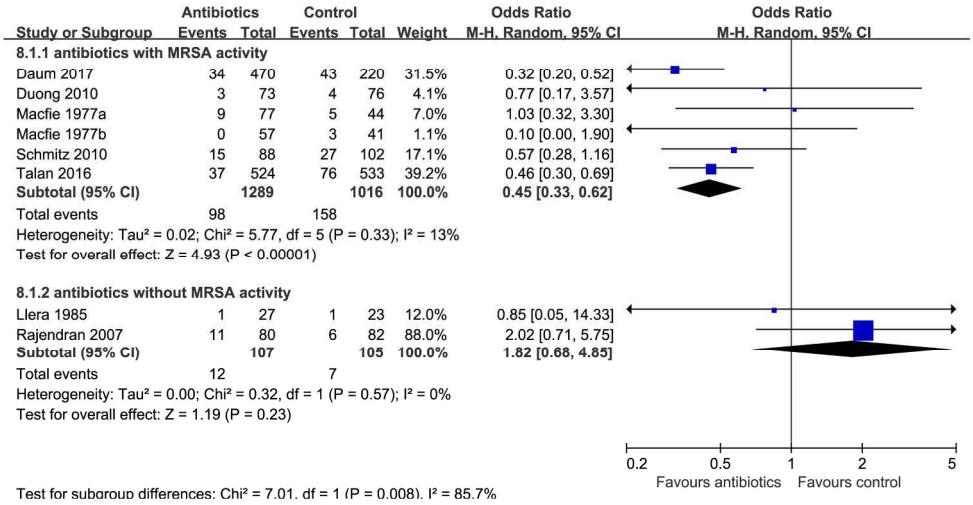

Fig 5 Subgroup analysis of treatment failure within 1 month by antibiotics with vs without MRSA activity

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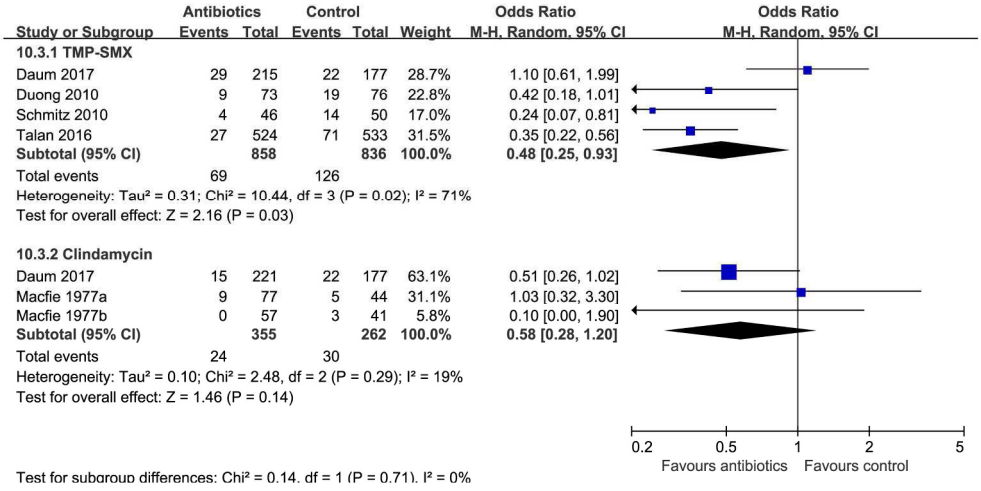

Fig 6 Subgroup analysis of recurrence by type of antibiotics (TMP-SMX versus clindamycin)

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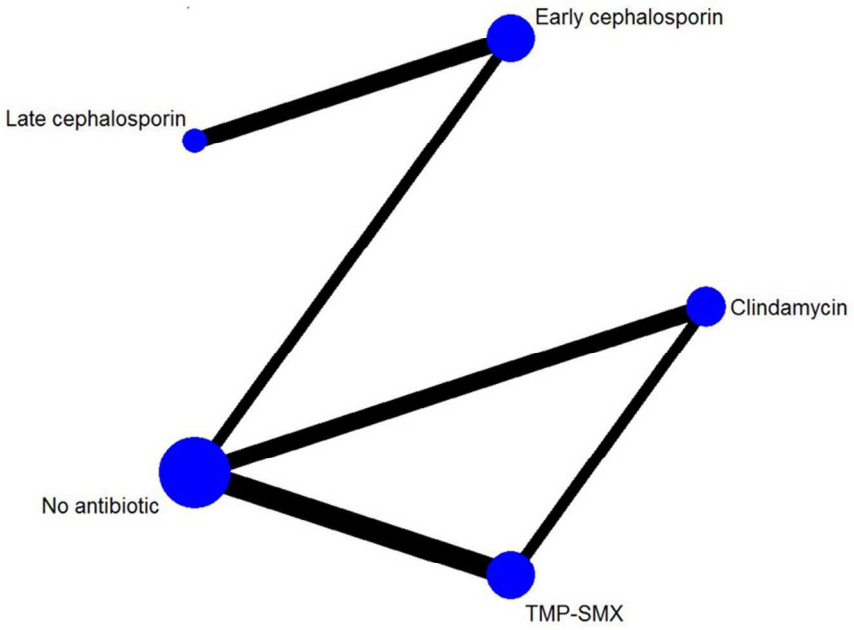

Fig 7 Network of included RCTs with available direct comparisons for treatment failure within 1 month.

80x59mm (300 x 300 DPI)

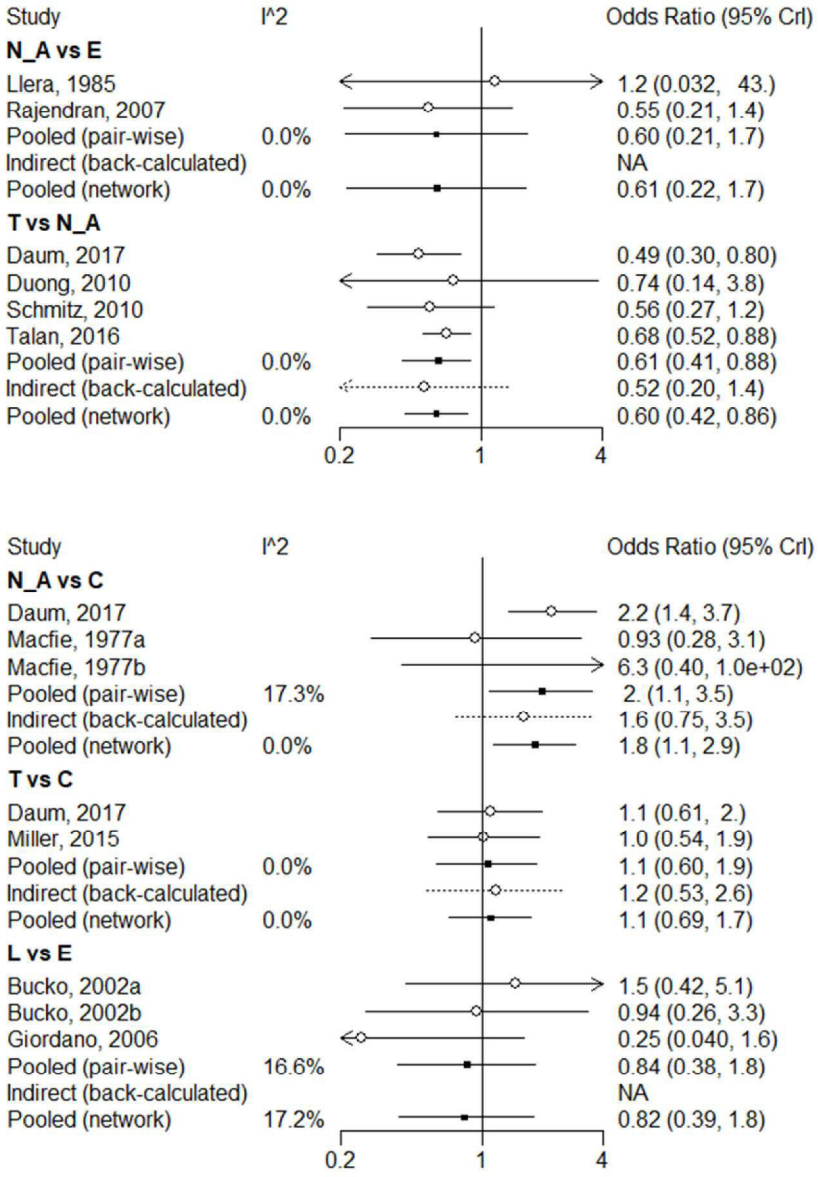

Fig 8 Forest plot of network meta-analysis results for treatment failure within 1 month.

244x343mm (300 x 300 DPI)

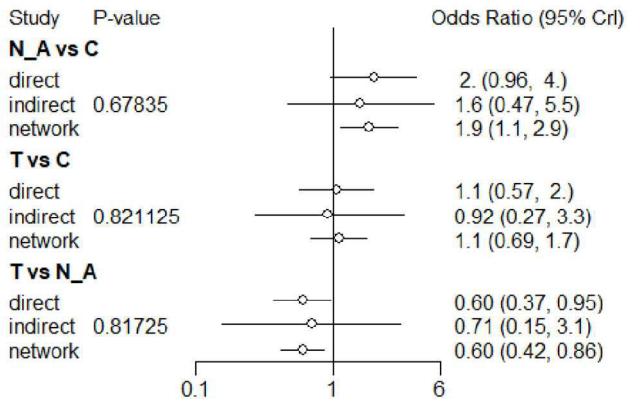

Fig 9 Assessment of network consistency, for all comparisons for which pairwise and indirect estimates were possible.

125x99mm (300 x 300 DPI)

Appendix 1 Search strategies

1. Medline (Ovid) (Search date: August 17, 2017)

1 exp abscess/
2 abscess* mp.
3 boil mp.
4 furunc* mp.
5 carbunc*mp.
6 1 or 2 or 3 or 4 or 5
7 exp skin diseases, infectious/
8 skin mp.
9 cutaneous mp.
10 superficial mp.
11 face mp.
12 facial mp.
13 7 or 8 or 9 or 10 or 11 or 12
14 6 and 13
15 exp anti-infective agents/
16 antibiotic* mp.
17 antimicrobial* mp.
18 antibacterial*.mp.
19 trimethoprim-sulfamethoxazole.mp.
20 clindamycin.mp.
21 cephalexin.mp.
22 cefazolin.mp.
23 doxycycline.mp.
24 minocycline.mp.
25 daptomycin.mp.
26 vancomycin.mp.
27 linezolid.mp.
28 nafcillin.mp.
29 dicloxacillin.mp.
30 televancin.mp.
31 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 clinical trial.mp.
33 clinical trial.pt.
34 random:.mp.
35 tu.xs.
36 33 or 34 or 35 or 36
37 14 and 32 and 37
38 limit 37 to humans

2. Embase (Ovid) (Search date: August 17, 2017)

1 exp skin abscess/

2 ((abscess* or boil or furunc* or carbunc*) adj6 (skin or cutaneous or superficial or face or facial)).mp.
3 1 or 2
4 exp antiinfective agent/
5 antibiotic*.mp.
6 antimicrobial*.mp.
7 antibacterial*.mp.
8 trimethoprim-sulfamethoxazole.mp.
9 clindamycin.mp.
10 cephalexin.mp.
11 cefazolin.mp.
12 doxycycline.mp.
13 minocycline.mp.
14 daptomycin.mp.
15 vancomycin.mp.
16 linezolid.mp.
17 nafcillin.mp.
18 dicloxacillin.mp.
19 televancin.mp.
20 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21 random:.mp.
22 clinical trial:.mp.
23 exp health care quality/
24 21 or 22 or 23
25 3 and 20 and 24

3. Cochrane Central Register of Controlled Trials (Ovid) (Search date: August 7, 2017)

1 exp abscess/
2 abscess*.mp.
3 boil.mp.
4 furunc*.mp.
5 carbunc*.mp.
6 1 or 2 or 3 or 4 or 5
7 exp skin diseases, infectious/
8 skin.mp.
9 cutaneous.mp
10 superficial.mp.
11 face.mp.
12 facial).mp.
13 7 or 8 or 9 or 10 or 11 or 12
14 6 and 13
15 exp Anti-Infective Agents/
16 antibiotic*.mp.
17 antimicrobial*.mp.

18 antibacterial*.mp.
19 trimethoprim-sulfamethoxazole.mp.
20 clindamycin.mp.
21 cephalexin.mp.
22 cefazolin.mp.
23 doxycycline.mp.
24 minocycline.mp.
25 daptomycin.mp.
26 vancomycin.mp.
27 linezolid.mp.
28 nafcillin.mp.
29 dicloxacillin.mp.
30 televancin.mp.
31 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

4. ClinicalTrials.gov (Search date: October 31, 2017)

skin infection OR abscess OR abscesses | Studies With Results

Appendix 2

Table A Inclusion criteria of abscess and definition of treatment failure/cure as reported in the included trials

Author (year)	Inclusion criteria of abscesses	Definition of treatment failure/cure
RCTs comparing antibiotics versus placebo or standard care		
Daum 2017[9]	A single abscess (defined as a circumscribed, drainable collection of pus) with a greatest diameter of 5.0 cm or less (≤3 cm for participants 6 to 11 months of age and ≤4 cm for participants 1 to 8 years of age), evidenced by two or more of the following signs or symptoms for at least 24 hours: erythema, swelling or induration, local warmth, purulent drainage, and tenderness to pain or palpation.	A lack of clinical cure was defined as lack of resolution of signs or symptoms of the infection, an inability to continue taking the study agent because of adverse effects within the first 48 hours, or any one of the following: recurrence at the original site of infection or occurrence of a skin infection at a new body site, unplanned surgical treatment of the skin infection, or hospitalization related to the infection.
Duong 2010[24]	Skin abscesses and were nontoxic, with temperature less than 38.4 °C, skin abscess included the presence of all of the following features: (1) acute onset within 1 week, (2) fluctuance,(3) erythema, (4) induration, and (5) tenderness, with or without purulent drainage.	Treatment failure was defined as the presence of any of the signs or symptoms (erythema, warmth, induration, fluctuance, tenderness, and drainage) at the 10-day follow-up or worsening signs or symptoms before the 10-day follow-up requiring further surgical drainage, change in medication, or hospital admission for intravenous antibiotics. New lesions within 5 cm of the original abscess site were also considered treatment failures. New lesions may consist of folliculitis, furuncles, carbuncles, or abscesses.
Llera 1985[25]	Localized collection of pus causing a fluctuant soft tissue swelling and surrounded by firm granulation tissue and erythema.	It considered treatment failure if any sign of fluctuance, drainage, induration, warmth, or tendemess was present at seven days.

Macfie 1977[28]	Acute superficial abscesses	A recurrence was recorded first, if a further collection of pus appeared at the same site as the original incision, and secondly, if signs of infection, discharge or inflammation reappeared or persisted and became worse following incision.
Rajendran 2007[27]	Diagnostic criteria for an abscess:(1) acute onset within 7 days prior to enrollment; (2) purulent drainage or purulent aspirate; (3) erythema, induration (≥2 cm in diameter), or tenderness; and (4) evidence of lobulated fluid at time of enrollment	Clinical cure: at the 1-week follow-up visit if there was resolution of the following signs and symptoms: purulent wound drainage, erythema, fluctuance, localized warmth, pain/tenderness, and edema/induration Treatment failure, defined as the presence of any of those above symptoms.
Schmitz 2010[26]	Uncomplicated skin abscesses requiring incision and drainage	Treatment failure defined as no improvement after 2 days, development of a new separate lesion or worsening infection (required evidence of an increased diameter of abscess or cellulitis, or the presence of fever or systemic response) within 7 days, leading to an intervention.
Talan 2016[10]	A fluctuant and/or indurated lesion, or findings of a fluid-filled cavity on soft tissue ultrasound evaluation that, when opened reveals purulent material, receiving I&D and having a minimum diameter (along any axis) of at least 2 cm (measured from the borders of induration, if a fluctuant lesion, or borders of the abscess cavity on ultrasound, if not fluctuant)	Clinical failure was defined as fever, an increase in the maximal dimension of erythema by >25% from baseline, or worsening of wound swelling and tenderness by the visit during the treatment period (day 3 or 4); fever, no decrease in the maximal dimension of erythema from baseline, or no decrease in swelling or tenderness by the visit at the end of the treatment period (day 8–10); and fever or more than minimal erythema, swelling, or tenderness by the test-of-cure visit (day 14–21).
RCTs comparing alternative antibiotics		
Bucko 2002[29]	Mild to moderate uncomplicated skin or skin structure infections, at least 2 of the following local signs and symptoms: pain, tenderness, swelling, erythema, associated warmth, purulent drainage/discharge, induration, and regional lymph node swelling or tenderness	Patients were considered clinical cures if their pretreatment signs and symptoms of infection had improved or resolved and they did not need additional antibiotic therapy for the treatment of the skin or skin structure infection clinical failures: at the post treatment visit if they experienced either persistent or worsening signs and symptoms or an improvement only after the patient received additional antimicrobial therapy for the infection.

Giordano 2006[30]	A mild to moderate uncomplicated skin or skin structure infections, which included, but was not limited to, cellulitis, erysipelas, impetigo, simple abscess, wound infection, furunculosis, and folliculitis	Patients were considered clinical failure if they experienced persistent or worsening signs and symptoms, had onset of new USSSI signs/symptoms at the baseline infection site following at least 72 h of antibiotic therapy, or needed additional antimicrobial therapy for the skin infection.
Keiichi 1982[33]	Suppurative skin and soft tissue infections	No details provided
Miller 2015[32]	Patients with uncomplicated skin infections who had two or more of the following signs or symptoms for 24 or more hours: erythema, swelling or induration, local warmth, purulent drainage, and tenderness to pain or palpation. Abscess was defined as a circumscribed, drainable collection of pus.	A lack of clinical cure was defined as a lack of resolution of signs or symptoms of infection, the occurrence of side effects that necessitated discontinuation of treatment with the study medication within the first 48 hours, or any one of the following before the test-of-cure visit: occurrence of a skin infection at a new body site, unplanned surgical treatment of the skin infection, or hospitalization related to the infection.
Montero 1996[31]	Acute skin and/or soft tissue infections	Treatment failure was defined as no change in, or worsening of, signs and symptoms of infection.

USSSI= uncomplicated skin or skin structure infections

Table B Risk of bias of included randomised controlled trials

Author	Adequate randomisation sequence generation	Adequate allocation concealment	Blinding of participants	Blinding of caregivers	Blinding of outcome assessors	Infrequent missing outcome data‡
Bucko 2002a[29]	**Probably yes** Randomised, double-blind*	**Probably yes** Randomised, double-blind†	**Probably yes** Double-blind (details not reported)	**Probably yes** Double-blind (details not reported)	**Probably yes** Double-blind (details not reported)	**Probably yes** There were 8.9% (26/291), 9.2% (26/283), 6.4% (18/283) patients with missing data for cure rate at TOC in three groups, respectively
Bucko 2002b[29]	**Probably yes** Randomised, double-blind	**Probably yes** Randomised, double-blind	**Probably yes** Double-blind (details not reported)	**Probably yes** Double-blind (details not reported)	**Probably yes** Double-blind (details not reported)	**Probably yes** There were 7.2% (20/278), 6.5%(18/277), 9.2%(25/273) patients with missing data for cure rate at TOC in three groups, respectively
Daum 2017[9]	**Definitely yes** Variable-block randomisation was performed by an independent statistics and data-coordinating center	**Definitely yes** Variable-block randomisation was performed by an independent statistics and data-coordinating center	**Definitely yes** Participants and all study staff were unaware	**Definitely yes** Participants and all study staff were unaware	**Definitely yes** Participants and all study staff were unaware	**Probably no** There were 10.5% (28/266), 11.8% (31/263), 14.3% (37/257) patients with missing data in three groups for cure rate at TOC, respectively; **Definitely no** There were 12.0% (32/266), 14.1% (37/263), 15.2% (39/257) patients with missing data for cure rate at 1 month in three groups, respectively

Duong 2010[24]	**Definitely yes** Computer randomisation	**Probably yes** Randomised, double-blind	**Definitely yes** The patient, parents, and clinician who assessed the clinical outcome were blinded to group assignment	**Definitely yes** The patient, parents, and clinician who assessed the clinical outcome were blinded to group assignment	**Definitely yes** The patient, parents, and clinician who assessed the clinical outcome were blinded to group assignment	**Probably yes** There were 9.6% (8/84) and 5.1% (4/77) patients in control and TMP groups with missing data for 10d treatment failure rate, respectively; **Definitely no** 37.3% (36/77) and 41.0% (32/84) patients in TMP and control groups with missing data for 30d new lesions, respectively
Giordano 2006[30]	**Definitely yes** Computer randomisation	**Probably yes** Details not reported, investigator-blinded	**Definitely no** Investigator-blinded	**Definitely yes** Investigator-blinded	**Probably yes** Investigator-blinded	**Probably no** There were 10.9% (21/192) and 13% (26/200) patients in Cefdinir and Cephalexin groups with missing data for cure rate at TOC, respectively
Keiichi 1982[33]	**Probably yes** Randomised, double-blind	**Probably yes** Randomised, double-blind	**Probably yes** Double-blind (details not reported)	**Probably yes** Double-blind (details not reported)	**Probably yes** Double-blind (details not reported)	**Definitely yes** Follow up rate was 100%
Llera 1985[25]	**Probably yes** Randomised, double-blind	**Probably yes** Randomised, double-blind	**Definitely yes** The patient, examining physician, or investigators were blinded to group assignment.	**Definitely yes** The patient, examining physician, or investigators were blinded to group assignment.	**Definitely yes** The patient, examining physician, or investigators were blinded to group assignment.	**Definitely no** There were (31/81) 38% with missing outcome data in two groups

Macfie 1977[28]	**Probably yes** Details not reported, open-label	**Probably no** Details not reported, open-label††	**Definitely no** Open-label	**Definitely no** Open-label	**Definitely no** Open-label	**Probably no** Details not reported
Miller 2015[32]	**Definitely yes** Variable-block randomisation was performed by an independent statistics and data-coordinating center	**Definitely yes** Performed by an independent contract research organization (EMMES) that developed the randomisation code	**Definitely yes** Participants and all study staff were unaware of the study-group assignments	**Definitely yes** Participants and all study staff were unaware of the study-group assignments	**Definitely yes** Participants and all study staff were unaware of the study-group assignments	**Probably no** There were 8.6% (7/127) and 11.3% (13/115) patients with abscess in Clindamycin and TMP-SMX groups with missing data for cure rate at TOC, respectively
Montero 1996[31]	**Probably yes** Details not reported, open-label	**Probably no** Open-label	**Definitely no** Open-label	**Definitely no** Open-label	**Definitely no** Open-label	**Definitely yes** There were 2% (2/100) and 2% (2/100) patients azithromycin and cefaclor groups with missing data for 10-14d treatment failure, respectively
Rajendran 2007[27]	**Definitely yes** A block randomisation scheme	**Probably yes** Sequentially numbered, sealed envelopes	**Definitely yes** All patients, investigators, and clinic staff were blinded to study group assignment	**Definitely yes** All patients, investigators, and clinic staff were blinded to study group assignment	**Definitely yes** All patients, investigators, and clinic staff were blinded to study group assignment	**Definitely yes** There were 2.4% (2/82) and 2.4% (2/84) patients in cephalexin and control groups with missing data for 7d treatment failure, respectively

Schmitz 2010[26]	**Definitely yes** A block randomisation scheme	**Definitely yes** Sealed envelopes	**Definitely yes** Patients and physicians were blinded to treatment	**Definitely yes** Patients and physicians were blinded to treatment	**Definitely yes** Patients and physicians were blinded to treatment	**Probably no** There were 8.3% (8/96) and 12.1% (14/116) patients in TMP/SMX and control groups with missing data for 7d treatment failure, respectively; **Definitely no** There were 52.1% (50/96) and 56.9% (66/116) patients in TMP/SMX and control groups with missing data for 30d new lesions, respectively
Talan 2016[10]	**Definitely yes** Web-based randomisation	**Definitely yes** Using double-blind, Web-based randomisation	**Definitely yes** The treatment arms masked to both the subject and the study staff	**Definitely yes** The treatment arms masked to both the subject and the study staff	**Definitely yes** The treatment arms masked to both the subject and the study staff	**Definitely no** There were 15.3% (96/629) and 16.7% (106/636) patients in placebo and TMP-SMX groups with missing data for cure rate at TOC, respectively

* Method for generating randomisation sequence not clearly reported. We judged that generating randomisation sequence was likely achieved regardless of blinding methods according to instructions. We followed this rule throughout the review.

† Method for allocation concealment not clearly reported. We judged that concealed allocation was likely achieved given it was a randomised double blinded trial, according to instructions. We followed this rule throughout the review.

†† Method for allocation concealment not clearly reported. We judged that concealed allocation was unlikely achieved given it was a randomised open label trial, according to instructions. We followed this rule throughout the review.

‡ We used the following rules to judge the infrequent missing outcome data for all included trials throughout the review: definitely yes: there were less than 5% patients with missing outcome data, and missing outcome data were generally balanced across treatment groups, with similar reasons for missing data across groups; probably yes: there were 5 to 10% patients with missing outcome data, and missing outcome data were generally balanced across treatment groups, with similar reasons for missing data across groups; probably no: there were 10% to 15% of missing outcome data; definitely no: there were over 15% patients with missing outcome data, or there were more than 5% absolute difference of missing outcome data between groups.

Table C Safety profile of antibiotics versus placebo or usual care

Outcomes	No. of trials	Events/total		OR(95%CI)	P value of test for overall	I^2	Tau^2	P value of interaction
		Antibiotics	Placebo or usual care					
Over all gastrointestinal side effects								
TMP-SMX vs Placebo	4	303/1064	252/1072	1.28(1.04, 1.58)	0.02	0%	0.00	0.05
Clindamycin vs Placebo	1	49/265	23/255	2.29(1.35, 3.88)	0.002	--	-	
Anaphylactic reaction*								
TMP-SMX vs Placebo	3	7/434	3/455	2.32(0.67,8.06)	0.19	28%	0.00	0.94
Clindamycin vs Placebo	1	7/265	3/255	2.17(0.62, 7.58)	0.22	--	-	
Nausea								
TMP-SMX vs Placebo	3	149/987	108/988	1.49(0.98,2.25)	0.06	11%	0.03	0.48
Clindamycin vs Placebo	1	6/265	6/255	0.96(0.31,3.02)	0.95	--	-	
Diarrhoea								
TMP-SMX vs Placebo	3	111/964	117/948	0.92(0.70,1.22)	0.56	0%	0.00	0.001
Clindamycin vs Placebo	1	43/265	17/255	2.71(1.50,4.89)	0.0009	--	-	

Sepsis*								
TMP-SMX vs Placebo	1	1/630	0/617	7.24(0.14,364.86)	0.32	-	-	
Death*								
TMP-SMX vs Placebo	2	1/891	1/872	0.98(0.06,15.68)	0.99	-	-	-
Clindamycin vs Placebo	1	0/265	0/255	-	-	-	-	

* Data were pooled using Peto's methods

Appendix 3 Sensitivity analyses for the comparison between antibiotics versus placebo/standard care

Table A Sensitivity analyses using alternative effect measures

Outcomes	No. of trials	Events/total		RR(95%CI)	P value	I^2	Tau^2
		Antibiotics	Placebo/ standard care	M-H, Random			
Treatment failure within 1 month							
Antibiotics vs Placebo	8	110/1396	165/1121	0.62(0.42,0.91)	0.02	48%	0.12
Recurrence within 1 month							
Antibiotics vs Placebo	6	93/1213	134/921	0.53(0.35,0.80)	0.003	45%	0.11
Late recurrence 1 to 3 months							
Antibiotics vs Placebo	2	96/550	140/561	0.72(0.54,0.97)	0.03	18%	0.01
Hospitalization							
Antibiotics vs Placebo	2	19/597	35/609	0.56(0.33,0.96)	0.04	0%	0.00
Gastrointestinal side effects							
TMP-SMX vs Placebo	4	303/1064	252/1072	1.18(1.03,1.34)	0.02	0%	0.00
Clindamycin vs Placebo	1	49/265	23/255	2.05(1.29,3.26)	0.002	-	-
Nausea							

TMP-SMX vs Placebo	3	149/987	108/988	1.44(0.91,2.28)	0.12	19%	0.06
Clindamycin vs Placebo	1	6/265	6/255	0.96(0.31,2.94)	0.95	-	-
Diarrhoea							
TMP-SMX vs Placebo	3	111/964	117/948	0.93(0.73,1.19)	0.57	0%	0.00
Clindamycin vs Placebo	1	43/265	17/255	2.43(1.43,4.15)	0.001	-	-
Anaphylaxis							
TMP-SMX vs Placebo	3	7/434	3/455	1.78(0.49,6.42)	0.38	0%	0.00
Clindamycin vs Placebo	1	7/265	3/255	2.25(0.59,8.59)	0.24	-	-
Death							
TMP-SMX vs Placebo	2	1/891	1/872	0.98(0.06,15.62)	0.99	-	-
Clindamycin vs Placebo	1	0/265	0/255	-	-	-	-
Sepsis							
TMP-SMX vs Placebo	1	1/630	0/617	2.94(0.12,71.99)	0.51	-	-

Table B Sensitivity analyses using alternative statistical model

Outcomes	No. of trials	Events/total		OR(95%CI)	P value	I^2
		Antibiotics	Placebo/ standard care	M-H, Fixed		
Late reccurence						
Antibiotics vs Placebo	2	96/550	140/561	0.64(0.48.0.85)	0.003	0%
Hospitalization						
Antibiotics vs Placebo	2	19/597	35/609	0.54(0.31,0.96)	0.03	0%
Gastrointestinal side effects						
TMP-SMX vs Placebo	4	303/1064	252/1072	1.30(1.05,1.60)	0.01	0%
Clindamycin vs Placebo	1	49/265	23/255	2.29(1.35,3.88)	0.002	-
Nausea						
TMP-SMX vs Placebo	3	149/987	108/988	1.44(1.10,1.90)	0.008	11%
Clindamycin vs Placebo	1	6/265	6/255	0.96(0.31,3.32)	0.95	-
Diarrhoea						
TMP-SMX vs Placebo	3	111/964	117/948	0.92(0.70,1.22)	0.56	0%
Clindamycin vs Placebo	1	43/265	17/255	2.71(1.50,4.89)	0.0009	-

Anaphylaxis	3	14/699	3/455	2.41(0.80,7.22)	0.12	0%
TMP-SMX vs Placebo	3	7/434	3/455	2.10(0.63,6.96)	0.23	0%
Clindamycin vs Placebo	1	7/265	3/255	2.28(0.58,8.91)	0.24	-

Table C Sensitivity analyses using alternative pooling method

Outcomes	No. of trials	Events/total		OR(95%CI)	P value	I^2	Tau^2
		Antibiotics	Placebo/ standard care	M-H, Random			
Hospitalization							
Antibiotics vs Placebo	2	19/597	35/609	0.54(0.31,0.96)	0.04	0%	0.00
Infections in family members							
TMP-SMX vs Placebo	1	20/504	34/509	0.58(0.33,1.02)	0.06	-	
Invasive infections (1 month)							
TMP-SMX vs Placebo	1	2/524	2/533	1.02(0.14,7.25)	0.99	-	
Invasive infections (3 month)							
TMP-SMX vs Placebo	1	1/504	0/509	3.04(0.12,74.70)	0.50	-	
Anaphylactic reaction							
TMP-SMX vs Placebo	3	7/434	3/455	1.80(0.49,6.58)	0.38	0%	0.00
Clindamycin vs Placebo	1	7/265	3/255	2.28(0.58, 8.91)	0.24	-	
Sepsis							
TMP-SMX vs Placebo	1	1/630	0/617	2.94(0.12,72.38)	0.51	-	

Death						
TMP-SMX vs Placebo	2	1/891	1/872	0.98(0.06,15.69)	0.99	-

Table D Sensitivity analyses using different inclusion criteria and different definition of treatment failure

Outcomes	No. of trials	Events/total		OR(95%CI)	P value	I^2	Tau^2
		Antibiotics	Placebo/ standard care	M-H, Random			
Sensitivity analyses by omiting trials exclusively reporting recurrence							
Treatment failure within 1 month	6	101/1262	157/1036	0.56 (0.35,0.90)	0.02	53%	0.16
Sensitivity analyses by omiting trials with patients treated by primary suture							
Treatment failure within 1 month	7	101/1319	160/1077	0.54 (0.34,0.86)	0.010	49%	0.16
Recurrence within 1 month	5	84/1136	129/877	0.43 (0.27,0.71)	0.0008	45%	0.13
Sensitivity analyses by omiting trials published before 1990							
Treatment failure within 1 month	5	100/1235	156/1013	0.56 (0.34,0.93)	0.03	62%	0.19
Recurrence within 1 month	4	84/1079	126/836	0.45 (0.27,0.74)	0.002	51%	0.13

Table E Sensitivity analyses using alternative methods of random effects meta-analysis

Outcomes	No. of trials	Events/total		OR (95%CI)	P value
		Antibiotics	Placebo/ standard care	HKSJ	
Treatment failure within 1 month					
Antibiotics vs Placebo	8	110/1396	165/1121	0.58 (0.33,1.01)	0.05
Recurrence within 1 month					
Antibiotics vs Placebo	6	93/1213	134/921	0.48 (0.26,0.88)	0.03
Late recurrence 1 to 3 month					
Antibiotics vs Placebo	2	96/550	140/561	0.64 (0.10,4.08)	0.20
Hospitalization					
Antibiotics vs Placebo	2	19/597	35/609	0.54 (0.19,1.56)	0.09
Gastrointestinal side effects					
TMP-SMX vs Placebo	4	303/1064	252/1072	1.28 (0.92,1.78)	0.10
Nausea					
TMP-SMX vs Placebo	3	149/987	108/988	1.49 (0.58,3.82)	0.21
Diarrhoea					
TMP-SMX vs Placebo	3	111/964	117/948	0.92 (0.74,1.15)	0.25

Anaphylaxis					
TMP-SMX vs Placebo	3	7/434	3/455	1.80(0.13,24.56)	0.44

HKSJ=Hartung-Knapp-Sidik-Jonkman

Table F Sensitivity analyses using different assumptions about missing data

Assumptions	No. of trials	Events/total		OR(95%CI)	P value	I^2	Tau^2
		Antibiotics	Placebo/ standard care				
Treatment failure within 1 month							
None has event*	8	110/1597	165/1293	0.59 (0.38,0.91)	0.02	46%	0.15
All had event†	8	311/1597	337/1293	0.71 (0.51,0.97)	0.03	46%	0.08
Best case scenario††	8	110/1597	337/1293	0.28 (0.15,0.53)	<0.0001	78%	0.52
Worst case scenario‡	8	311/1597	165/1293	1.59 (0.97,2.60)	0.07	68%	0.26
Worst plausible analysis #	8	183/1597	191/1293	0.82 (0.56,1.19)	0.30	44%	0.29
Recurrence within 1 month							
None has event*	6	93/1472	134/1171	0.52 (0.30,0.89)	0.02	57%	0.22
All had event†	6	352/1472	384/1171	0.62 (0.48,0.79)	0.0002	27%	0.02
Best case scenario††	6	93/1472	384/1171	0.15 (0.07,0.31)	<0.00001	82%	0.58
Worst case scenario‡	6	352/1472	134/1171	2.02 (0.96,4.24)	0.06	86%	0.62
Worst plausible analysis	6	193/1472	177/1171	0.83 (0.53,1.29)	0.4	61%	0.16
Later recurrence 1 to 3 month							
Worst plausible analysis #	2	187/713	178/713	1.48 (0.55,3.96)	0.44	87%	0.45

***Hospitalizations*§**							
Worst plausible analysis #	2	39/713	41/713	0.94 (0.60,1.47)	0.78	0%	0.00
Pain (tenderness) (3 to 4 days)							
Worst plausible analysis #	1	337/636	352/629	0.89 (0.71,1.11)	0.29	-	
Pain (tenderness) (8 to 10 days)							
Worst plausible analysis #	1	63/636	64/629	0.97 (0.67,1.40)	0.87	-	
Additional surgical procedures							
Worst plausible analysis #	1	97/636	85/629	1.15 (0.84,1.58)	0.38	-	

* All the participants lost to follow up did not have the event;

†All the participants lost to follow up had the event;

†† None of those lost to follow-up in the treatment group had the event and all those lost to follow-up in the control group did;

‡ All participants lost to follow-up in the treatment group had the event and none of those in the control group did;

Worst plausible analysis: Meta-analysis using the plausible most stringent $RI_{MPD/FU}$ (the incidence of outcome events in participants with missing data relative to those with complete follow-up). We defined a constant $RI_{MPD/FU}$ of 1.0 for control group missing participants, and 1.5, 2, 3, 5 for antibiotics group when the event rate was >40%, 30-40%, 10-30%, <10% respectively.

§ Pooled data using Peto's methods

Appendix 4

Table A GRADE judgements for NMA of antibiotics for skin abscesses*

		Direct evidence								Indirect evidence								Network estimate			
Treatment 1	Treatment 2	Risk of bias	Inconsistency	Indirectness	Publication bias	Direct rating without imprecision	Direct is more precise than indirect	imprecision	Direct rating with imprecision	Common comparator(s)	Treatment 1 vs common first comparator	Middle comparison	Treatment 2 vs common final comparator	Lowest of direct common comparisons	Intransitivity	Indirect rating without imprecision	Imprecision	Indirect rating with imprecision	Higher rating of direct and indirect without Incoherence	Imprecision	Network rating final
No Abx	Early C	No	No	No	No	**High**	NA	-1	**Mod**										High	NA	-1 **Mod**
No Abx	Late C									Early C	High	NA	High	High	No	**High**	-2	**Low**	High	NA	-2 **Low**
No Abx	TMP/SMX	-1	No	No	No	**Mod**	Yes	No	**Mod**	Clinda.	High	NA	High	High	No	**High**	-2	**Low**	High	No	No **Mod**
No Abx	Clinda.	-1	No	No	No	**Mod**	Yes	-1	**Mod**	TMP/SMX	High	NA	High	High	No	**High**	-2	**Low**	High	No	No **Mod**
Early C	Late C	No	No	No	No	**High**	NA	-1	**Mod**										High	NA	-1 **Mod**
Early C	TMP/SMX									No Abx	High	NA	High	High	No	**High**	-1	**Mod**	High	NA	-1 **Mod**
Early C	Clinda.									No Abx	High	NA	High	High	No	**High**	-1	**Mod**	High	NA	-1 **Mod**
Late C	TMP/SMX									Early C/No Abx	High	High	High	High	No	**High**	-1	**Mod**	High	NA	-1 **Mod**
Late C	Clinda.									Early C/No Abx	High	High	High	High	No	**High**	-1	**Mod**	High	NA	-1 **Mod**
TMP/SMX	Clinda.	No	No	No	No	**High**	Yes	-1	**Mod**	No Abx	High	NA	High	Mod	No	**High**	-2	**Low**	High	No	No **High**

No Abx, no antibiotics; Early C, early generation (1st/2nd) cephalosporins; later generation (3rd/4th) cephalosporins; TMP/SMX, trimethoprim/sulfamethoxazole; Clinda., clindamycin; Mod, Moderate; -1, rated down once because of serious concerns; -2, rated down twice because of very serious concern

*GRADE certainty ratings can be high, moderate, low, or very low. All comparisons started at high certainty and then were rated down if there were concerns with the GRADE domains listed. 'No' means that we judged there to not be any serious concerns with that domain for that comparison. '-1' means that we rated down the certainty by one category because of serious concerns and '-2= means that we rated down the certainty by two categories because of very serious concerns. For a detailed explanation of the GRADE domains and process for rating comparisons within a network meta-analysis, please see Puhan MA, et al. *BMJ.* 2014;349:g5630.

		included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	*9*
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	8-9
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	9
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	*8-9*
RESULTS†			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	*14*
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	*14-15*
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	*12–15*
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	*12-15*
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	*14-15*
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	11
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	*13-14*
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	16-17

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	20