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Antistreptococcal interventions for guttate and chronic plaque psoriasis (Review)

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[Intervention Review]

Antistreptococcal interventions for guttate and chronic plaque psoriasis

Gwendy Dupire[1,2], Catherine Droitcourt[3,4], Carolyn Hughes[5], Laurence Le Cleach[6,7]

[1]Department of Immuno-Allergology, CHU Brugmann, Brussels, Belgium. [2]Department of Dermatology, Hôpital Universitaire Des Enfants Reine Fabiola, Brussels, Belgium. [3]Department of Dermatology, Université de Rennes 1, Rennes, France. [4]Clinical Investigation Center, CIC-P 0203, INSERM, Pharmacoepidemiology Unit, Université de Rennes 1, Rennes, France. [5]c/o Cochrane Skin Group, The University of Nottingham, Nottingham, UK. [6]Department of Dermatology, Hôpital Henri Mondor, Créteil, France. [7]Epidemiology in dermatology and evaluation of therapeutics (EpiDermE) - EA 7379, Université Paris Est Créteil (UPEC), Créteil, France

Contact: Gwendy Dupire, Department of Immuno-Allergology, CHU Brugmann, Place A.Van Gehuchten 4, Brussels, 1020, Belgium. gwendy.dupire@gmail.com.

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ABSTRACT

Background

Psoriasis is a chronic skin disease that affects approximately two per cent of the general population. Plaque psoriasis is the most common form: it usually appears as raised, red patches of inflamed skin, covered with silvery white scales. The patches often occur in a symmetrical pattern. Guttate psoriasis is a particular form of psoriasis with widespread, small erythematosquamous lesions. *Streptococcal* infection is suspected to be a triggering factor for the onset of guttate psoriasis, and flare-up of chronic plaque psoriasis. The previous Cochrane Review on this topic was published in 2000; it required an update because antistreptococcal treatment continues to be used to treat psoriasis, especially for the acute form of guttate psoriasis.

Objectives

To assess the effects of antistreptococcal interventions for guttate and chronic plaque psoriasis.

Search methods

We searched Cochrane Skin Specialised Register, Cochrane Register of Studies Online, CENTRAL, MEDLINE, Embase, LILACS, and five trials registers (January 2019). We checked the reference lists of included and excluded studies and searched conference proceedings from the American Academy of Dermatology, Society for Investigative Dermatology, and European Academy of Dermatology and Venereology.

Selection criteria

We considered randomised controlled trials (RCTs) assessing antistreptococcal interventions (tonsillectomy or systemic antibiotic treatment) in people with clinically diagnosed acute guttate and chronic plaque psoriasis compared with placebo, no intervention, or each other.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Primary outcome measures were: 1) time-to-resolution; achieving clear or almost clear skin (Physician Global Assessment (PGA) 0 or 1 or Psoriasis Area and Severity Index (PASI) 90 or 100); 2) proportion of participants with adverse effects and severe adverse effects. Secondary outcomes were: 1) proportion of participants achieving clear or almost clear skin; 2) proportion of participants achieving PASI 75 or PGA 1 to 2; 3) risk of having at least one relapse at long-term follow-up. Short-term assessment was defined as within eight weeks of the start of treatment; long-term was at least one year after the start of treatment.

Main results

We included five trials (162 randomised participants); three were conducted in a hospital dermatology department. One study declared funding by a pharmaceutical company. Participants' ages ranged from 12 to 77 years; only two participants were younger than 15 years. Mean PASI score at baseline varied from 5.7 (i.e. mild) to 23 (i.e. severe) in four studies. Twenty-three of 162 participants had *streptococcus*-positive throat swab culture. We did not perform a meta-analysis due to heterogeneity of participants' characteristics and interventions.

None of the trials measured our efficacy primary outcome, time-to-resolution, or the secondary outcome, risk of having at least one relapse at long-term follow-up.

We rated the quality of the results as very low-quality evidence, due to high risk of bias (absence of blinding of participants and caregivers, and high risk of outcome reporting bias) and imprecision (single study data with a low number of events). Hence, we are very uncertain about the results presented.

Guttate psoriasis

One three-armed trial (N = 43) assessed penicillin (50,000 international units (IU)/kg/day in three doses) versus erythromycin (250 mg four times per day) versus no treatment (treatment for 14 days, with six-week follow-up from start of treatment). Adverse events and the proportion of participants achieving clear or almost clear skin were not measured.

One trial (N = 20) assessed penicillin (1.6 MU (million units) intramuscularly once a day) versus no treatment (six weeks of treatment, with eight-week follow-up from start of treatment). At six-week (short-term) follow-up, no adverse events were observed in either group, and there was no statistically significant difference between the two groups in the proportion of participants with clear or almost clear skin (risk ratio (RR) 2.00, 95% confidence interval (CI) 0.68 to 5.85).

One trial (N = 20) assessed rifampicin (300 mg twice daily) versus placebo (14-day treatment duration; six-week follow-up from start of treatment); none of the review outcomes were measured.

These trials did not measure the proportion of participants achieving PASI 75 or PGA 1 to 2.

Chronic plaque psoriasis

One trial (N = 50) assessed long-term azithromycin treatment (500 mg daily dose) versus vitamin C. Adverse events were reported in the azithromycin group (10 out of 30 had nausea and mild abdominal upset), but not in the vitamin C group. The proportion of participants who achieved clear or almost clear skin was not measured. In the azithromycin group, 18/30 versus 0/20 participants in the vitamin C group reached PASI 75 at the end of 48 weeks of treatment (RR 25.06, 95% CI 1.60 to 393.59).

One trial (N = 29) assessed tonsillectomy versus no treatment, with 24-month follow-up after surgery. One participant in the tonsillectomy group had minor bleeding. At eight-week follow-up, 1/15 in the tonsillectomy group, and 0/14 in the no treatment group achieved PASI 90; and 3/15 participants in the tonsillectomy group, and 0/14 in the no treatment group achieved PASI 75 (RR 6.56, 95% CI 0.37 to 116.7).

Authors' conclusions

We found only five trials (N = 162), which assessed the effects of five comparisons (systemic antibiotic treatment (penicillin, azithromycin) or tonsillectomy). Two comparisons (erythromycin compared to no treatment, and rifampicin compared to placebo) did not measure any of the outcomes of interest. There was very low-quality evidence for the outcomes that were measured, Therefore, we are uncertain of both the efficacy and safety of antistreptococcal interventions for guttate and chronic plaque psoriasis.

The included trials were at unclear or high risk of bias and involved only a small number of unrepresentative participants, with limited measurement of our outcomes of interest. The studies did not allow investigation into the influence of *Streptococcal* infection, and a key intervention (amoxicillin) was not assessed.

Further trials assessing the efficacy and tolerance of penicillin V or amoxicillin are needed in children and young adults with guttate psoriasis.

PLAIN LANGUAGE SUMMARY

Does treating *Streptococcal* throat infection help improve psoriasis?

Review question

We wanted to find out how well treatments for infections caused by the *Streptococcus* bacteria worked, and how safe they were, when compared with no treatment, placebo (an identical but inactive treatment), or each other, in people with acute guttate or chronic plaque psoriasis.

Background

Chronic plaque psoriasis is a long-term condition that causes patches of red, flaky skin, covered with scales (called plaques); it is the most frequent form of psoriasis, and is more common in adults.

Guttate psoriasis is characterised by smaller lesions, and is more common in children and young people. Some studies have suggested that guttate psoriasis occurs in less than 30% of people with psoriasis.

The cause of psoriasis is unknown, but *Streptococcal* infection may trigger guttate psoriasis or flare-ups of chronic plaque psoriasis.

Tonsillectomy may prevent or reduce the severity of throat infections, and limit the *Streptococcus* reservoir. Antibiotics work by destroying the bacteria that appear to trigger psoriasis.

Study characteristics

The evidence is current to January 2019.

We included five studies (162 participants); three were conducted in hospital dermatology departments. Participants were 12 to 77 years old (100 males; 62 females). One study was funded by a pharmaceutical company. The severity of the condition ranged from mild to severe. *Streptococcus* bacteria were found in the throats of 14% of people.

We classed outcomes measured within eight weeks of the start of treatment as short-term, and those measured at least one year after the start of treatment as long-term. The antibiotic trials in guttate psoriasis patients were all short-term in duration; the antibiotic trial in chronic plaque psoriasis was 48 weeks long.

Three studies included participants with guttate psoriasis, and assessed the short-term effects of antibiotics: penicillin (20 participants), or erythromycin compared to no treatment (43 participants), and rifampicin compared to placebo (20 participants).

Two studies included participants with chronic plaque psoriasis. One study assessed azithromycin (antibiotic) versus vitamin C at 48 weeks (50 participants); one assessed tonsillectomy versus no intervention at eight weeks and 24 months (29 participants).

Key results

These results are backed by very low-quality evidence, so we are not certain of their accuracy. Each result is based on only one study.

No studies measured our main outcome of interest, the time taken for the skin to be clear or almost clear of lesions, or the risk of relapsing at least once during long-term follow-up.

No side effects were seen when penicillin was compared with no treatment in people with guttate psoriasis. Side effects were not measured for the comparisons of rifampicin versus placebo, or erythromycin versus no treatment.

In participants with chronic plaque psoriasis, one trial assessed azithromycin versus vitamin C, and 10 participants in the azithromycin group complained of nausea or mild stomach upset. A trial of tonsillectomy versus no treatment reported one case of minor bleeding in the tonsillectomy group.

Two studies in participants with chronic plaque psoriasis measured the number of participants achieving a 75% reduction on the Psoriasis Area and Severity Index (PASI 75). In one, 18/30 participants in the azithromycin group reached PASI 75 versus none in the vitamin C group. In the other, 3/15 in the tonsillectomy group reached PASI 75 versus none in the no treatment group. The guttate psoriasis trials did not assess this outcome.

We are uncertain whether the number of participants with guttate psoriasis achieving clear or almost clear skin differs between those given penicillin and those receiving no treatment. Only one participant with chronic plaque psoriasis achieved almost clear skin in the tonsillectomy group compared to none in the no treatment group. The other three trials did not measure this outcome.

Quality of the evidence

Many of our main outcomes were not assessed. Those that were assessed were based on very low-quality evidence, meaning we are not sure of their accuracy. The studies were very small, and had a high risk of bias because participants and trial assessors were aware of treatment allocation. More studies are needed to see if antibiotic treatment of *Streptococcal* infection shortens the duration of acute guttate psoriasis, stopping it from turning into a long-term condition (chronic plaque psoriasis).

Summary of findings for the main comparison. Penicillin compared to no treatment for guttate psoriasis

Penicillin compared to no treatment for guttate psoriasis						
Patient or population: guttate psoriasis **Setting**: inpatients in department of dermatology **Intervention:** penicillin **Comparison:** no treatment						
Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with no treatment	**Risk with Penicillin**				
Time-to-resolution: achieving PASI 90 to 100 or PGA 0 to 1	-	-	-	-	-	Not measured
Proportion of participants with adverse events and severe adverse events Follow-up: 6 weeks	See comment	See comment	-	20 (1 RCT)	⊕⊝⊝⊝ VERY LOW [1]	It was specified that no adverse events were observed in either group.
Proportion of participants achieving clear or almost clear skin (PASI 90 to 100 or PGA 0 to 1) Follow-up: 6 weeks	300 per 1000	600 per 1000 (204 to 1000)	RR 2.00 (0.68 to 5.85)	20 (1 RCT)	⊕⊝⊝⊝ VERY LOW [2]	Study authors state that no difference was observed between baseline and 6 weeks for psoriasis severity (PASI).
Proportion of participants achieving PASI 75 or PGA 1 to 2	-	-	-	-	-	Not measured in either trial. PASI assessment results were only presented as mean PASI at 6 weeks. No difference was observed between the two groups in either trial.
Risk of having at least one relapse at long-term follow-up	-	-	-	-	-	No long-term follow-up

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality/certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality/certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality/certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality/certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded by three levels to very low certainty. Evidence was downgraded by two levels due to risk of bias. The study was at high risk of bias as the study was not blinded. The study was at unclear risk of bias for selective outcome reporting (no primary outcome stated). Evidence was downgraded further by one level due to imprecision: the study included few participants (N = 20).
[2]Downgraded by three levels to very low certainty. Evidence was downgraded by two levels due to risk of bias. The study was at high risk of bias as the study was not blinded and clinical assessment of psoriasis severity was subjective. The study was at unclear risk of bias for selective outcome reporting (no primary outcome stated). Evidence was downgraded further by one level due to imprecision: the study included few participants (N = 20).

Summary of findings 2. Erythromycin compared to no treatment for guttate psoriasis

Erythromycin compared to no treatment for guttate psoriasis

Patient or population: guttate psoriasis

Setting: inpatients in department of dermatology
Intervention: erythromycin
Comparison: no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with erythromycin				
Time-to-resolution: achieving PASI 90 to 100 or PGA 0 to 1	-	-	-	-	-	Not measured
Proportion of participants with adverse events and severe adverse events	-	-	-	-	-	Not measured
Proportion of participants achieving clear or almost clear skin (PASI 90 to 100 or PGA 0 to 1)	-	-	-	-	-	Not measured

Proportion of participants achieving PASI 75 or PGA 1 to 2	-	-	-	-	-	Not measured Results were only reported as mean PASI at baseline and at 6 weeks. No difference was found between groups for mean PASI at 6 weeks.
Risk of having at least one relapse at long-term follow-up	-	-	-	-	-	Not measured

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality/certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality/certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality/certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality/certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Summary of findings 3. Azithromycin compared to vitamin C for chronic plaque psoriasis

Azithromycin compared to vitamin C for chronic plaque psoriasis

Patient or population: chronic plaque psoriasis
Setting: outpatients of department of dermatology

Intervention: azithromycin
Comparison: vitamin C

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with vitamin C	Risk with azithromycin				
Time-to-resolution: achieving PASI 90 to 100 or PGA 0 to 1	-	-	-	-	-	Not measured

Proportion of participants with adverse events and severe adverse events Follow-up: 48 weeks	See comment	See comment	-	50 (1 RCT)	-	Nausea and mild abdominal upset were reported in 10/30 in the azithromycin group. There was no mention of the presence or absence of adverse events in the Vitamin C group.
Proportion of participants achieving clear or almost clear skin (PASI 90 to 100 or PGA 0 to 1)	-	-	-	-	-	Not measured
Proportion of participants achieving PASI 75 or PGA 1 to 2 Follow-up: 48 weeks	See comment	See comment	RR 25.06 (1.60 to 393.59)	50 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1]	18/30 participants in the azithromycin group versus 0/20 in the vitamin C group.
Risk of having at least one relapse at long-term follow-up	-	-	-	-	-	Not measured

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality/certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality/certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality/certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality/certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded by three levels to very low certainty: 2 levels due to unclear risk of bias for selective reporting (any primary outcome was specified) and high risk of bias for incomplete outcome data, and a further one level due to imprecision (one small study, wide confidence interval)

Summary of findings 4. Rifampicin compared to placebo for guttate psoriasis

Rifampicin compared to placebo for guttate psoriasis
Patient or population: guttate psoriasis **Setting**: not reported **Intervention:** rifampicin **Comparison:** placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with rifampicin				
Time-to-resolution: achieving PASI 90 to 100 or PGA 0 to 1	-	-	-	-	-	Not measured
Proportion of participants with adverse events and severe adverse events	-	-	-	-	-	Not measured
Proportion of participants achieving clear or almost clear skin (PASI 90 to 100 or PGA 0 to 1)	-	-	-	-	-	Not measured However, no change in psoriasis severity was observed in any group at 14 days and 6 weeks.
Proportion of participants achieving PASI 75 or PGA 1 to 2	-	-	-	-	-	Not measured
Risk of having at least one relapse at long-term follow-up	-	-	-	-	-	Not measured

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality/certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality/certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality/certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality/certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Summary of findings 5. Tonsillectomy compared to no intervention for chronic plaque psoriasis

Tonsillectomy compared to no intervention for guttate or chronic plaque psoriasis
Patient or population: chronic plaque psoriasis

Setting: not reported
Intervention: tonsillectomy
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with tonsillectomy				
Time-to-resolution: achieving PASI 90 to 100 or PGA 0 to 1	-	-	-	-	-	Not measured
Proportion of participants with adverse events and severe adverse events Follow-up: 8 weeks	See comment	See comment	RR 2.81 (0.12 to 63.83)	29 (1 RCT)	⊕⊝⊝⊝ VERY LOW [1]	One participant had minor bleeding in the tonsillectomy group. No adverse events in the no treatment group.
Proportion of participants achieving clear or almost clear skin (PASI 90 to 100 or PGA 0 to 1) Follow-up: 8 weeks	See comment	See comment	RR 2.81 (0.12 to 63.83)	29 (1 RCT)	⊕⊝⊝⊝ VERY LOW [1]	No events in the control group.
Proportion of participants achieving PASI 75 or PGA 1 to 2 Follow-up: 8 weeks	See comment	See comment	RR 6.56 (0.37 to 116.7)	29 (1 RCT)	⊕⊝⊝⊝ VERY LOW [1]	No events in the control group.
Risk of having at least one relapse at long-term follow-up	-	-	-	-	-	Not measured

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality/certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality/certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality/certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality/certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded by three levels to very low certainty: two levels due to risk of bias (participant and caregiver were not blinded; subjective outcome) and one further level due to imprecision (only one study, small number of participants)

BACKGROUND

For an explanation of terms we used in this review, please see Table 1.

Description of the condition

Psoriasis is a common, chronic inflammatory disorder that primarily affects the skin, and sometimes the joints. Guttate psoriasis is a particular form of psoriasis, characterised by a distinct clinical presentation with widespread small (0.5 to 1.5 cm) erythematosquamous lesions, located mainly on the trunk. It has an acute onset and a possibility of spontaneous resolution. Plaque psoriasis is the most common form of psoriasis. It typically appears as raised and well-demarcated red areas of inflamed skin covered with silvery white scales; it often shows a symmetrical distribution on the body. Antibiotics or tonsillectomy have been proposed as treatments for guttate psoriasis or flares of chronic plaque psoriasis; these treatments were introduced on the basis of the suspected relationship between infections with beta-haemolytic *Streptococci* (which can cause a throat infection, and more rarely perianal *Streptococcal* dermatitis) and acute manifestations of psoriasis (Telfer 1992).

Epidemiology

Psoriasis affects approximately two per cent of the general population, with equal distribution between the sexes (Parisi 2013). There are several forms of psoriasis, and different clinical presentations can be observed in the same person, either simultaneously or over time. Among these, chronic plaque psoriasis (psoriasis vulgaris) accounts for 90% of cases (Griffiths 2007). The prevalence of guttate psoriasis has not been clearly reported, but several studies cite a prevalence of less than 30% among people with psoriasis (Kundakci 2002; Kwon 2012; Rigopoulos 2010; Valenzuela 2011).

Clinical presentation and natural history

Chronic plaque psoriasis presents as erythematous plaques, which have a precise outline. They have a scaly surface. The plaques are usually located on the elbows, the knees, and the scalp, but the nails, hands, feet, and trunk are also frequently affected sites. Plaque size can vary from a minimal area to coverage of the entire body (Wolff 2009). Plaque psoriasis is a chronic disease with severity fluctuation over time. It is more common in adults than in children, with an increasing incidence with age up to around 40 years, and a second peak at around 50 to 59 years (Parisi 2013).

Guttate psoriasis is an eruptive form of psoriasis, with small lesions and a greater tendency toward spontaneous resolution. It typically appears in young adults and children with no previous history of psoriasis, where it is referred to as 'acute guttate psoriasis' (Mercy 2013). Sometimes, it occurs in people who already have chronic plaque psoriasis, where it is called a 'guttate flare of chronic psoriasis' (Chalmers 2001). Although guttate psoriasis is usually considered a form of psoriasis with a better prognosis, few studies have evaluated its long-term clinical course.

Based on limited data, guttate psoriasis is considered a form that resolves spontaneously after a few months (Ko 2010), from which one- to two-thirds of participants will subsequently develop a form of chronic plaque psoriasis (Ko 2010; Martin 1996; Williams 1976). There is little information on the rate at which people develop a chronic form of psoriasis after experiencing a first episode of acute guttate psoriasis. Rates of chronic plaque psoriasis after a first episode of guttate psoriasis vary in different studies: Martin 1996 found 33% of people developed it within 10 years after a first episode of guttate psoriasis; Ko 2010 found 36% developed chronic plaque psoriasis within six years; and Williams 1976 found 68% developed chronic plaque psoriasis within one year. The risk of recurrence of guttate psoriasis after a first resolved episode is also unknown. Mean time to disease clearance was 3.9 ± 2.4 months (Ko 2010).

The diagnosis of cutaneous psoriasis is clinical. A skin biopsy can be used to confirm the diagnosis in difficult cases.

Pathophysiology

The pathogenesis of psoriasis is still not fully known. An inflammatory immune response involving T lymphocytes, dendritic cells, neutrophils, and keratinocytes leads to a rapid turnover of skin renewal and histological inflammatory infiltrate, characteristic of psoriasis (Newman 2008).

Psoriasis occurs in people with a genetic predisposition (Elder 2010). Factors that can exacerbate it include skin trauma, smoking, alcohol, emotional stress, or drugs (Berth-Jones 2005). Pathogens, notably beta-haemolytic *Streptococci*, are considered to be triggering factors (Picciani 2013). A nested case-control study on a database from the United Kingdom examined exposure to systemic antibacterial prescriptions and infections within two years prior to a diagnosis of psoriasis in children with newly diagnosed psoriasis (N = 845) compared with age- and sex-matched controls (N = 8450). Infections of skin (adjusted odds ratio (aOR) 1.5, 95% confidence interval (CI) 1.2 to 1.7) and other sites (aOR 1.3, 95% CI 1.1 to 1.6) were associated with newly diagnosed psoriasis in children (Horton 2016). The link between acute guttate psoriasis and flares of chronic plaque psoriasis and *Streptococcal* infection is suspected but not proven.

Infections with beta-haemolytic *Streptococci*, which can cause a throat infection, and more rarely, perianal *Streptococcal* dermatitis (Ledoux 2009), may lead to acute guttate psoriasis, and are also suspected to cause flares of chronic plaque psoriasis (Gudjonsson 2003). (Where we refer to *Streptococcal* or *Streptococcus* in this section, we specifically mean beta-haemolytic *Streptococci*.) In one study, streptococci were isolated from the throats of 97% of people with guttate psoriasis (Tervaert 1970), while in two earlier studies, serologic evidence of recent *Streptococcal* infection was found in 56% and 85% of people (Norrlind 1955; Whyte 1964). In a prospective study, 58% of people with acute guttate psoriasis versus 26% of people with guttate exacerbations of chronic psoriasis had serologic evidence for recent *Streptococcal* infection (Telfer 1992). A relationship between *Streptococci* and chronic plaque psoriasis was also proposed in a prospective study, in which people with psoriasis reported a sore throat 10 times more often than controls in the same household, and *Streptococcal* throat infections could cause exacerbation of chronic plaque psoriasis (Gudjonsson 2003). However, as serological evidence is no longer considered a relevant test, the strength of the conclusions of these studies became weaker (Shulman 2012). In addition to these studies that highlighted an association without established causality, in vitro studies put forward the superantigen theory to explain the interaction between psoriasis and infection (Abe 1991; Kotzin 1993; Leung 1995; Valdimarsson 1997). Some

bacteria are superantigens, which means that they are able to trigger multiple immune reactions, leading to the stimulation of different T cells and activation of cytokines (Kotzin 1993). A recent study showed the direct involvement of *Streptococcal* infection in pathological mechanisms of psoriasis, such as interleukin 17 (IL-17) production and epidermal cell activation: *Streptococcal* throat extracts (isolated from the throats of participants with psoriatic), added to the cultures of epidermal cells, which were obtained by skin biopsy of psoriatic lesions, led to the activation of circulating psoriatic cutaneous lymphocyte–associated antigen memory T cells (Ferran 2013).

Description of the intervention

Antistreptococcal interventions include tonsillectomy or antibiotic treatment. These antistreptococcal treatments are not recommended in current guidelines; however, these guidelines addressed only chronic plaque psoriasis in adulthood, except the NICE guideline, in which phototherapy is recommended for acute guttate psoriasis (NICE 2017).

Tonsillectomy

Tonsillectomy is a surgical procedure during which the tonsils are removed; it is carried out under general anaesthesia. Recurrent acute pharyngitis and chronic tonsillitis are the most common reasons for tonsillectomy in adults. A Cochrane Review showed a modest benefit of tonsillectomy or adenotonsillectomy in the treatment of recurrent acute tonsillitis in children (Burton 2009). Most published studies refer to a paediatric population, and the small amount of information available about adult sore throat and the effect of tonsillectomy suggests that surgery is beneficial, but the evidence for this is not robust (Laing 1991; Paradise 1984; SIGN 2010). Tonsillectomy is associated with morbidity that includes possible hospitalisation, the risk of anaesthesia, and prolonged throat pain; there are also financial costs to consider (SIGN 2010). Bleeding during or after surgery is not uncommon, and there may be other complications (Baugh 2011).

Antibiotics

Antibiotics are recommended for acute sore throat, or for those with chronic recurrent sore throat. Treatment for people with Group A *Streptococcal* (GAS) pharyngitis, recommended by the Infectious Diseases Society of America (IDSA), is 10 days of: phenoxymethylpenicillin (penicillin V) 250 mg four times daily or 500 mg twice daily; or amoxicillin 50 mg/kg once daily (maximum of 1000 mg) or 25 mg/kg (maximum of 500 mg) twice daily (Shulman 2012; Tanz 2007).

For the treatment of GAS, few antibiotic regimens have been evaluated prospectively in randomised controlled trials, and in the literature, there are a few studies about the eradication of *Streptococcal* transmission (Shulman 2012). The most common adverse effects of antibiotics are gastrointestinal disorders. However, rare serious adverse effects, which are sometimes life-threatening, such as a bacterial overgrowth (pseudomembranous colitis by overgrowth of *Clostridium difficile* bacteria) or allergic reactions (anaphylactic shock, Stevens-Johnson syndrome, or toxic epidermal necrolysis), are also described. At the population level, the use of antibiotics must be limited because of the emergence of bacterial resistance to antibiotics (Baugh 2011; Burton 2009; Shulman 2012; SIGN 2010).

Treatments recommended for chronic plaque psoriasis are topical therapy (topical corticosteroids or vitamin D analogues, or both), phototherapy, and systemic therapy (non-biological or biological). In current practice, some physicians prescribe antibiotics for acute guttate psoriasis in a context of pre-existing or concomitant infection, mainly pharyngitis, as first-line treatment, or in addition to recommended treatments. However, surveys carried out in different countries, and studies of the prescribing patterns of dermatologists, general practitioners, or paediatricians for children with psoriasis, did not mention the use of antibiotic therapy (Augustin 2013; De Jager 2009; Mahe 2018; Vogel 2012).

How the intervention might work

It is thought that by eradicating *Streptococcus*, antistreptococcal interventions will stop the superantigen activity of *Streptoccocus*, which is suspected of triggering the immune reactions responsible for psoriasis, and so may improve or clear an acute flare of guttate psoriasis, and decrease or inhibit flares of chronic plaque psoriasis.

Removing the tonsils, which are a site of *Streptococcus* infection and a *Streptococcus* reservoir, may prevent throat infections, reduce the severity of throat infections, or limit the *Streptococcus* reservoir (Burton 2009).

Why it is important to do this review

Despite the fact that guidelines on psoriasis no longer recommend the use of antistreptococcal interventions (SIGN 2010), antibiotics continue to be perceived as a good treatment option, especially for the acute form of guttate psoriasis. This is because epidemiological and in vitro studies report arguments in favour of a link between psoriasis flare and *Streptococcal* infection. As the previous Cochrane Review is old, it is important to conduct a new assessment of the available evidence on the efficacy and safety of antistreptococcal interventions (Owen 2000). We chose to do this by drafting a new protocol because we changed the objectives and outcomes of the original review (Dupire 2015).

OBJECTIVES

To assess the effects of antistreptococcal interventions for guttate and chronic plaque psoriasis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), including multi-arm trials.

Types of participants

We included participants with clinically diagnosed acute guttate or chronic plaque psoriasis. In cases where studies only include a subset of relevant participants, we only included the study if the characteristics of participants and results were provided separately, or could be obtained through contact with authors.

Types of interventions

We considered any antistreptococcal antibiotic therapies, or tonsillectomy compared with placebo or no intervention, or comparisons between each other.

Types of outcome measures

Primary outcomes

1. Time to resolution (time between inclusion and resolution), where resolution was defined as participants achieving clear or almost clear skin (Physician Global Assessment (PGA) 0 or 1; or Psoriasis Area and Severity Index (PASI) 90, which refers to at least 90% reduction, or PASI 100, which refers to 100% reduction in the PASI score)
2. Proportion of participants with adverse effects, and severe adverse effects

Secondary outcomes

1. Proportion of participants achieving clear or almost clear skin (PGA 0 or 1 or PASI 90 or 100)
2. Proportion of participants achieving PASI 75 or PGA 1 to 2
3. Risk of having at least one relapse at long-term follow-up.

Timing of outcomes

By short-term, we mean within eight weeks of the start of treatment, and by long-term, we mean at least one year after the start of treatment.

Search methods for identification of studies

We aimed to identify all relevant RCTs, regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist searched the following databases up to 23 January 2019, using strategies based on the draft strategy for MEDLINE in our published protocol (Dupire 2015):

- the Cochrane Skin Specialised Register, using the search strategy in Appendix 1;
- the Cochrane Infectious Diseases Specialised Register and the Cochrane Sexually Transmitted Infections Specialised Register via the Cochrane Register of Studies Online (CRSO), using the strategy in Appendix 2;
- the Cochrane Central Register of Controlled Trials (CENTRAL) 2019, Issue 1, in the Cochrane Library, using the strategy in Appendix 3;
- MEDLINE Ovid (from 1946), using the strategy in Appendix 4;
- Embase Ovid (from 1974), using the strategy in Appendix 5; and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982), using the strategy in Appendix 6.

Trials registers

We searched the following trials registers, up to 24 January 2019, with the search term 'psoriasis':

- the ISRCTN registry (www.isrctn.com);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- the World Health Organization International Clinical Trials Registry Platform (ICTRP (apps.who.int/trialsearch/)); and
- the EU Clinical Trials Register (www.clinicaltrialsregister.eu).

Searching other resources

References from included studies

We checked the bibliographies of included and excluded studies for further references to relevant trials.

Contacting prominent authors in the field

We attempted to contact authors of included trials, in order to identify additional published or unpublished data.

Handsearching

We searched the following conference proceedings for years not included in the Cochrane Skin Specialised Register:

- American Academy of Dermatology (AAD) for 2008 and 2009, and from 2012 to 2016;
- Society for Investigative Dermatology (SID) from 2008 to 2016; and
- European Academy of Dermatology and Venereology (EADV) from 2008 to 2014.

Adverse effects

We did not perform a separate search for adverse effects of the target intervention. However, we examined data on adverse effects from the included studies we identified.

Data collection and analysis

We included 'Summary of findings' tables in our review for all comparisons, which we created with GRADEpro GDT software (GRADEpro GDT). In these, we summarised all of our primary and secondary outcomes (see section 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)).

Some parts of the methods section of this review uses text that was originally published in another Cochrane protocol (Le Cleach 2011).

Selection of studies

Two review authors (GD and CD) independently examined each title and abstract to exclude obviously irrelevant reports; they then independently examined the full text of potentially relevant articles to determine eligibility. These review authors discussed any disagreements with a third author (LLC) to reach consensus. We contacted study authors for clarification when necessary. We listed excluded studies, and document the primary reason for exclusion.

Data extraction and management

Two review authors (GD and CD) independently extracted the data from published and unpublished reports, using a standardised form. The team piloted this data extraction form on a set of included trials. A third author (LLC) was involved to resolve any disagreements on data extraction between the two review authors. We extracted from each included trial: study design, inclusion and exclusion criteria, baseline characteristics of the total number of participants randomised to each intervention, description of interventions and outcomes. We extracted these data to populate the 'Characteristics of included studies' tables. One review author (GD) checked and entered data into Review Manager 5 computer

software (Review Manager 2014). We contacted the authors of the studies to provide missing data when required.

Assessment of risk of bias in included studies

Two review authors (GD and CD) independently used Cochrane's 'Risk of bias' tool to assess the risk of bias of each of our included studies. They discussed disagreements with a third author (LLC) to reach consensus. We determined the risk of bias as 'low', 'high', or 'unclear' for each of the following domains, according to the general principles in section 8.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

Selection bias

- Was the allocation sequence adequately generated? We considered randomisation adequate if the allocation sequence was generated from a table of random numbers or by computer. We considered it inadequate if sequences could be related to prognosis. We considered it unclear if it was stated that the trial was randomised, but the method was not described.
- Was allocation adequately concealed? We deemed allocation concealment adequate if the report stated that it was undertaken by means of sequentially pre-numbered, sealed, opaque envelopes, or by a centralised system. We considered a double-blind double-dummy process at low risk of bias, even if the method of allocation concealment was not described.

Performance and detection bias

- Was knowledge of the allocated intervention adequately prevented during the study? We evaluated the risk of bias separately for personnel and participants, outcome assessors, and each outcome. In trials that compared pharmaceutical interventions (antibiotics) with placebo, if the presentation of the interventions was the same, we considered the blinding adequate, even in cases where there was no precise description of the blinding procedure.

Attrition bias

- Were incomplete outcome data adequately addressed? We examined if there was an imbalance across intervention groups in numbers or reasons for missing data, the types of measures undertaken to handle missing data, and whether the analysis was carried out on an intention-to-treat basis. We assessed the use of strategies to handle missing data.

Reporting bias

- Are reports of the study free of suggestion of selective outcome reporting? We evaluated whether each outcome was measured, analysed, and reported. We compared outcomes specified in study protocols (if available e.g. on trial registers), and in the methods sections, with outcomes presented in the results.

Other bias

We did not fulfil the 'other risk of bias' item, as we did not highlight particular circumstances leading to other risks of bias from particular trial designs, contamination between the experimental and control groups, or particular clinical settings.

Measures of treatment effect

For each pair-wise comparison and each dichotomous outcome, we used risk ratios (RR) with 95% confidence intervals (CI) as a measure of treatment effect.

For time-to-event outcomes, we had planned to combine estimates of log hazard ratios and standard errors obtained from results of Cox proportional hazards regression models, using the generic inverse-variance method; however, no time-to-event outcomes were available in the included trials.

Unit of analysis issues

The primary unit of analysis was the participant. We included only the first phase of cross-over studies because of the risk of carry-over bias and the unpredictable evolution of psoriasis, which may have an effect in subsequent phases.

Dealing with missing data

We extracted the number of randomised and analysed participants from each included trial. We requested missing data from trial authors or sponsors, by email. For missing data, we used simple imputation methods. We assumed that all missing data were either events or non-events (Higgins 2011).

Assessment of heterogeneity

We had planned to assess statistical heterogeneity by visual inspection of the forest plots and by calculating I^2 statistics. We had planned to interpret the I^2 statistic value according to the following thresholds (section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)):

- 0% to 40% might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity; and
- 75% to 100% represents considerable heterogeneity

Assessment of reporting biases

To address publication bias, we had planned to draw contour-enhanced funnel plots for each meta-analysis if 10 or more studies had contributed data to our outcomes (Egger 1997). We did not draw funnel plots because of the insufficient number of included studies.

Data synthesis

We had planned to undertake meta-analyses only if we judged participants, interventions, comparisons, and outcomes to be sufficiently similar. In cases of heterogeneity, we had planned to use a random-effects meta-analysis to combine studies. In cases of multi-arm trials, we had planned to combine groups to create a single pair-wise comparison. We had not planned to combine studies in a meta-analysis if the value of the I^2 statistic exceeded 75%, because this represents considerable heterogeneity. It was not possible to combine any data because of the small number of trials, and the absence of multiple trials comparing the same intervention and measuring our planned outcomes.

Subgroup analysis and investigation of heterogeneity

We had planned to investigate the influence of the presence, absence, or unknown status of an active *Streptococcal* infection at

the time of treatment onset, via subgroup analyses. According to the IDSA guidelines, cultures or rapid antigen detection tests (RADT) are recommended rather than antibody titers that only become positive several weeks after the end of infection. We considered the results of these tests for subgroup analyses (Shulman 2012).

We also planned to investigate the following two characteristics:

- guttate versus plaque psoriasis
- tonsillectomy versus antibiotic therapy.

In the absence of meta-analyses, we did not carry out any subgroup analyses.

Sensitivity analysis

For studies at higher risk of bias, we had planned to conduct sensitivity analyses. We had planned to perform sensitivity analysis to assess how sensitive the results were to reasonable changes in the assumptions we may have made with regard to missing data. In the absence of meta-analysis, we did not carry out any sensitivity analyses.

RESULTS

Description of studies

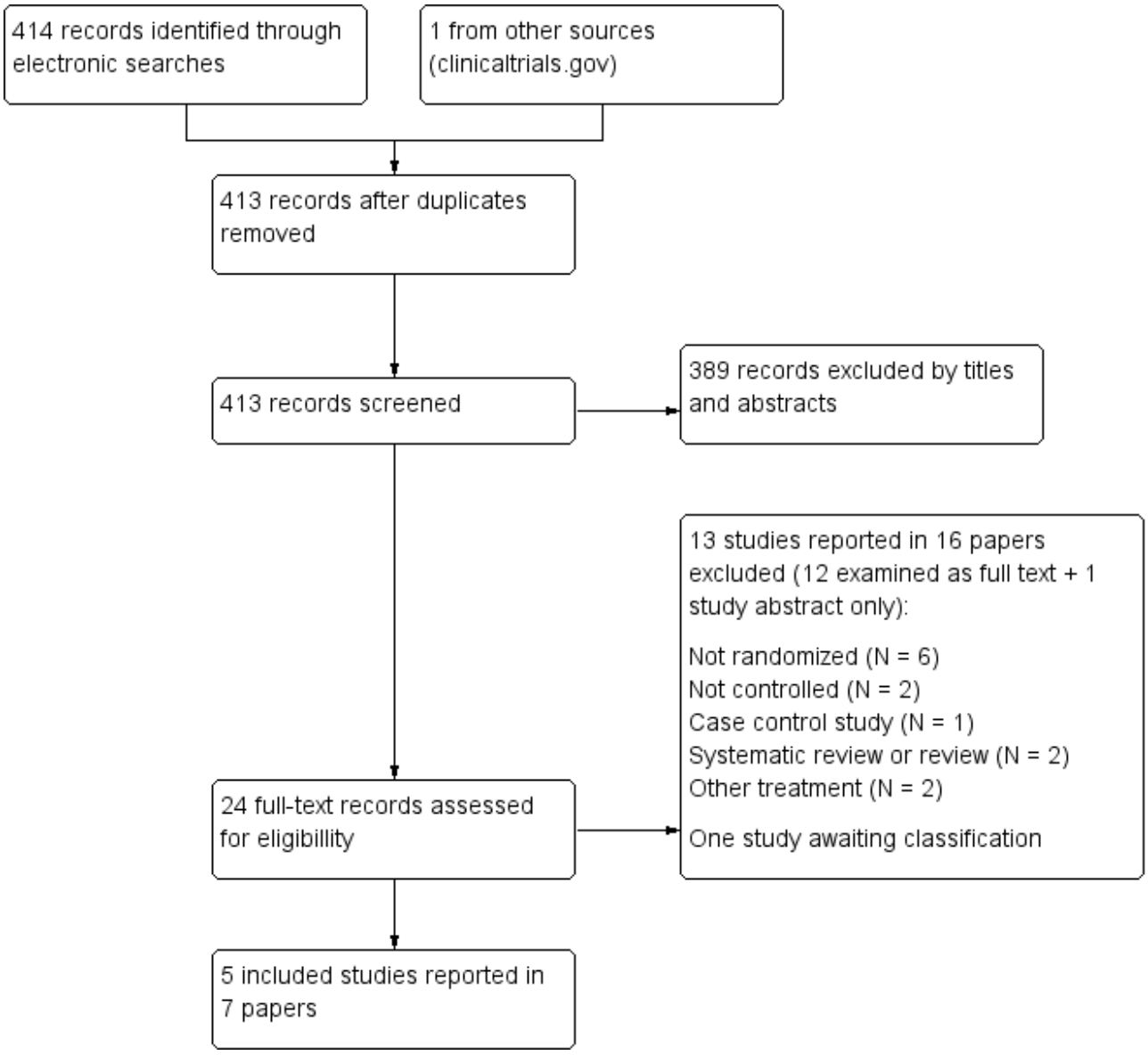
Results of the search

The searches of the electronic databases retrieved 414 records. The searches of other sources (e.g. handsearching conference proceedings, the Federal Drug Administration (FDA) reviews and the World Heatlh Organization (WHO) International Clinical Trials Registry Platform) identified one additional trial. After duplicate records were removed, we had 413 records.

We excluded 389 records based on titles and abstracts. We examined the full text of the remaining 24 citations. We excluded 13 studies reported in 16 papers; one was excluded based on the abstract as no full text could be obtained; see Characteristics of excluded studies (Masood 1997). We did not identify any relevant ongoing studies. We classified one study as awaiting classification; see Characteristics of studies awaiting classification. We included five trials, reported in seven papers; see Characteristics of included studies.

For a further description of our screening process, see the study flow diagram (Figure 1).

Figure 1. Flow diagram describing the searches and screening of studies



We obtained additional information via email for one trial (Thorleifsdottir 2012).

Included studies

We included five studies, involving 162 randomised participants; see the 'Characteristics of included studies' tables.

Trial design

All of the trials were parallel-arm trials: four trials assessed two arms and one trial included three arms (Dogan 2008). Three were single-centre trials (Caca-Biljanovska 2002; Dogan 2008; Thorleifsdottir 2012), one was a multicentric trial (two centres (Saxena 2010)), and the information was not reported in one (Vincent 1992). Trials were carried out in Turkey (Dogan 2008), the Republic of Macedonia (Caca-Biljanovska 2002), Iceland (Thorleifsdottir 2012), India (Saxena 2010), and for one, the information was not provided (Vincent 1992). Total duration of follow-up was six weeks (Dogan 2008; Vincent 1992) to eight weeks (Caca-Biljanovska 2002), for the three trials assessing guttate psoriasis; and 48 weeks (Saxena 2010) to two years (Thorleifsdottir 2012), for two trials assessing chronic plaque psoriasis.

One trial declared pharmaceuticals funding (Vincent 1992), one institutional funding (Thorleifsdottir 2012), one no funding (Saxena 2010); there was no information about funding for the other two trials. The setting described in three trials was a dermatology hospital department (Caca-Biljanovska 2002; Dogan 2008; Saxena 2010); the setting of the other two trials was not reported.

Participants

The mean number of participants randomised per trial was 32 (minimum 20 to maximum 50). A total of 92 participants were included in intervention arms, and 70 in placebo or no treatment arms.

Participants' age varied from 12 to 77 years.

In total, 62 participants were female and 100 were male; one trial included only men (Dogan 2008).

In three trials, all participants had guttate psoriasis (Caca-Biljanovska 2002; Dogan 2008; Vincent 1992); in two trials, all participants had chronic plaque psoriasis (Saxena 2010; Thorleifsdottir 2012).

Mean Psoriasis Area and Severity Index (PASI) score at baseline was 5.7, 10.6, 11.9, and 23 in Caca-Biljanovska 2002; Dogan 2008; Saxena 2010; Thorleifsdottir 2012, respectively, corresponding to mild, moderate, and severe psoriasis. The PASI score was not provided in Vincent 1992.

Four trials took throat swabs (Caca-Biljanovska 2002; Dogan 2008; Saxena 2010; Vincent 1992). All cultures of nose and throat swabs were negative in Caca-Biljanovska 2002; 8/43 (17%) were positive for *β-haemolytic streptococcus* in Dogan 2008, 1/20 participants were positive for *β-haemolytic Streptococcal* in Vincent 1992, and 14/29 were positive for *streptococcus* in Thorleifsdottir 2012 (additional information provided by the author by email). In one trial, the authors reported the results of the throat swab culture as equivocal (Saxena 2010).

Interventions

Systemic antibiotic therapy

Four trials assessed systemic antibiotic therapy; penicillin (1.6 MU (million units) given intermuscularly (IM) once a day for six weeks was compared to no treatment (Caca-Biljanovska 2002), oral azithromycin (500 mg daily dose, given orally for four days with a gap of 10 days, repeated 24 times) was compared to vitamin C (Saxena 2010), and oral rifampicin (300 mg twice daily given for 14 days) was compared to placebo (Vincent 1992). Oral erythromycin (250 mg four times a day) was compared to oral phenoxymethylpenicillin (50,000 IU/kg/d in three doses), and to no treatment for 14 days (Dogan 2008).

All of the participants in two trials received a co-intervention, namely topical betamethasone dipropionate 0.05% cream and phototherapy in Caca-Biljanovska 2002, and penicillin V or erythromycin 250 mg four times a day for 14 days in Vincent 1992.

The total duration of each trial was as follows: 8 weeks (Caca-Biljanovska 2002), 48 weeks (Saxena 2010), and 6 weeks (Dogan 2008; Vincent 1992).

Tonsillectomy

Tonsillectomy was compared to no intervention in one two-year long trial (Thorleifsdottir 2012). Topical or systemic psoriasis treatment was allowed, if needed by the participant.

Outcomes

Our primary outcome, time-to-achieve clear or almost clear status, was not reported in any included study. Adverse events were not reported in two trials (Dogan 2008; Vincent 1992), reported in only one group in another (Saxena 2010), and obtained through email contact with the author for one trial (Thorleifsdottir 2012); see Table 2 for details on study author contact.

Concerning our secondary outcomes, two of the five included trials reported the proportion of participants achieving clear or almost clear skin (Physician Global Assessment (PGA) 0 or 1, or PASI 90 or 100 (Caca-Biljanovska 2002; Thorleifsdottir 2012)), and the proportion of participants achieving PASI 75 or PGA 1 to 2 (Saxena 2010; Thorleifsdottir 2012). One reported partially on the risk of having at least one relapse at long-term follow-up (Thorleifsdottir 2012).

The primary outcome chosen by the study authors was not stated in four of the five trials, and was uncertain in one trial. One trial provided no information in the main publication, but we were able to obtain more information by contacting the study author, and by reading a secondary report on the study. The study author stated that the primary outcome was a reduction in the PASI score, with a coinciding decrease in the blood frequency of T lymphocytes, which recognise auto-antigens in the skin. However, in a secondary publication, the authors stated that the primary endpoints were defined as clinically significant changes in HRQoL (health-related quality of life), assessed by the Psoriasis Disability Index (PDI) and the Psoriasis Life Stress Inventory (PLSI), at 12 and 24 months (Thorleifsdottir 2012).

PASI was assessed in all trials, reported as the decrease of mean PASI scores from baseline in each group, or rate of PASI reduction, or rate of participants achieving PASI 75. Physician clinical assessment was assessed on a scale from 0 to 4, or 0 to 5 in two trials. No numerical results for efficacy assessment were available for one trial (Vincent 1992), and were presented only in figures, with no numerical data, for another (Thorleifsdottir 2012).

Excluded studies

Reasons for exclusion were described in the 'Characteristics of excluded studies' tables. We excluded 16 reports corresponding to 13 studies, for one of which, we were unable to obtain more than an abstract. The main reason for exclusion was absence of randomisation, which was true in seven of the excluded studies.

Studies awaiting classification

One study, registered in clinicaltrials.gov in 2007, comparing bicillin L-A to placebo in participants with chronic plaque psoriasis, was terminated in 2015 because there were "not enough enrollees to obtain". We were not able to find a report of the results or to contact the lead author, so we considered it to be awaiting classification (NCT00427609).

Ongoing study

We found no ongoing studies.

Risk of bias in included studies

We summarised 'Risk of bias' assessments in Figure 2 and Figure 3. All trials were at high risk of bias in at least two domains. Figure 2 presents our judgements about each risk of bias item, presented as percentages across all included studies. Figure 3 presents each risk of bias item for each included study.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

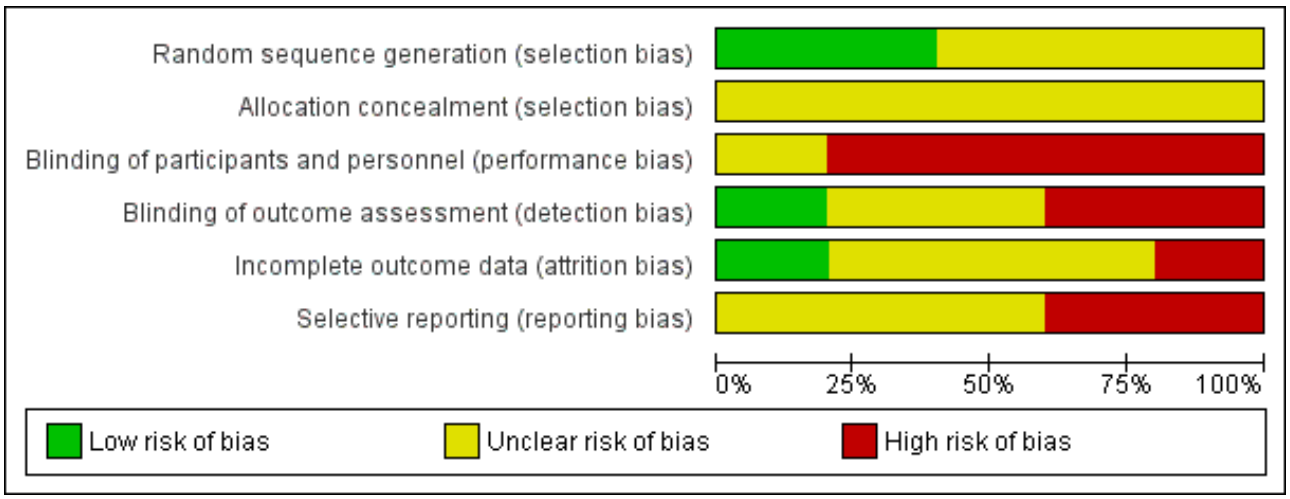
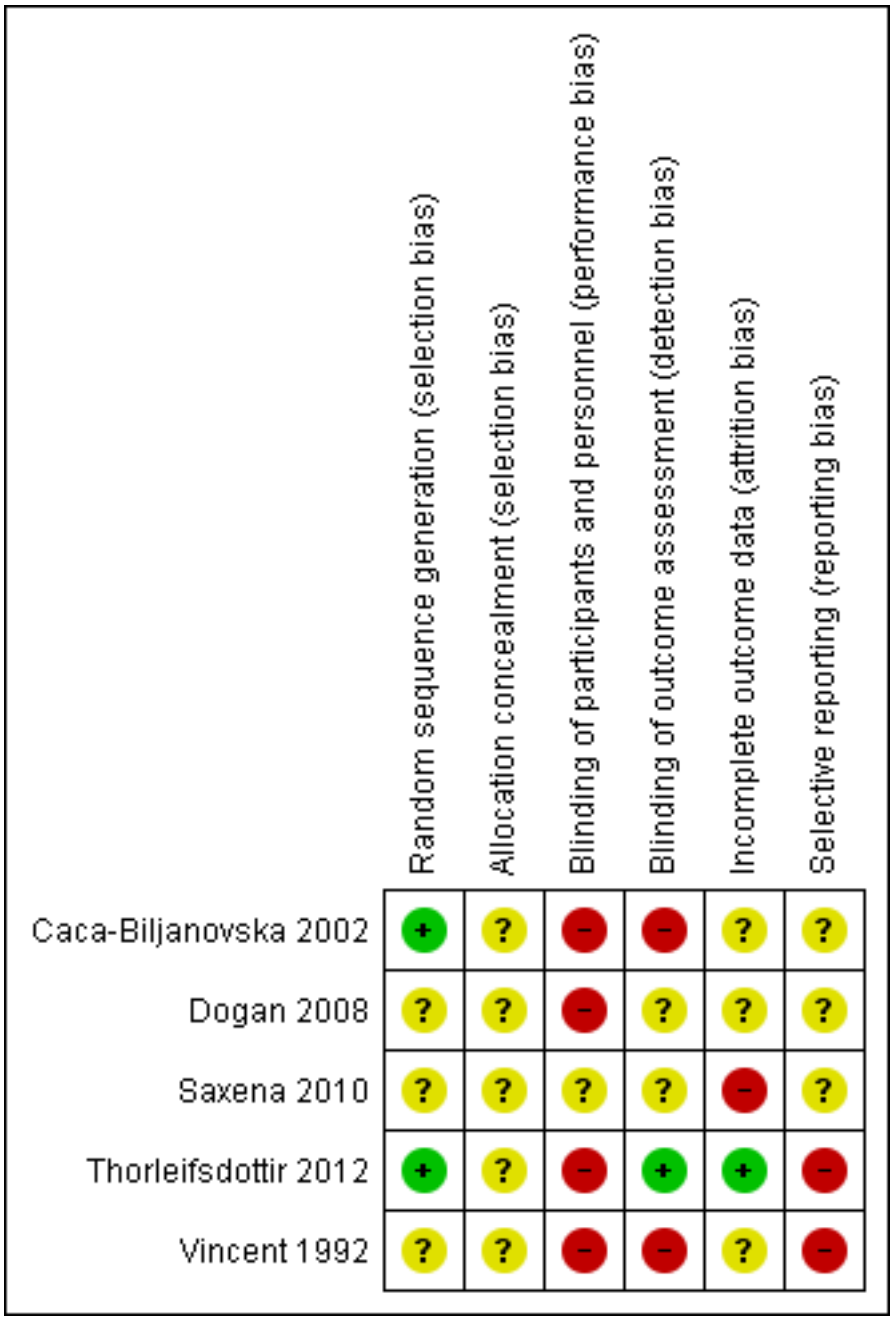


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Random sequence generation

Randomisation was never described as centralised. The report for three trials did not contain the description of the process of allocation sequence generation, and we considered them at unclear risk of bias for generation of sequence generation. In Saxena 2010, there was an important difference in PASI evaluation scores at baseline between groups that could be interpreted as a failure of the randomisation process. Sequence generation was reported, and was adequate for two others (Caca-Biljanovska 2002; Thorleifsdottir 2012).

Allocation concealment

Methods to guarantee allocation concealment were not reported in any of the five trials. Thus, we considered all trials at unclear risk of bias for allocation concealment.

Blinding

Performance bias

In four trials, participants and caregivers were presented as not blinded, and we considered them at high risk of bias. One trial was described as single blind, however, they did not clearly explain who was supposed to be blind, the participant or the assessor, and the comparator was not a real placebo, but a vitamin C tablet, so

we considered it was at unclear risk of bias for performance bias (Saxena 2010).

Detection bias

As all outcomes are subjective, absence of blinding was considered to be a high risk of bias. For two trials, the assessor was not blinded, and we considered them at high risk of detection bias (Caca-Biljanovska 2002; Vincent 1992). In two trials, the assessor was described as blinded; however as participants were not blinded, and no information was provided regarding specific measures undertaken to avoid communication on treatment between assessor, caregiver, and participants, we considered these trials at unclear risk of detection bias. We only considered one trial at low risk (Thorleifsdottir 2012).

Incomplete outcome data

We considered this item at unclear risk of bias for three trials, as no information on the number of withdrawals or the methods used to manage missing data was provided (Caca-Biljanovska 2002; Dogan 2008; Vincent 1992). We considered Saxena 2010 at high risk of bias, as an intention-to-treat analysis was not performed, and there was an unbalanced number of withdrawal between the two groups. One trial specified that no participant withdrew, and we considered it at low risk (Thorleifsdottir 2012).

Selective reporting

None of the included trials were registered in a trial registry. Four trials did not state the primary outcome. Among these, one did not report all the outcomes described in the methods section, and we considered it at high risk of bias for selective outcome reporting (Vincent 1992). We considered the three others at unclear risk of bias. For one study, the primary outcome was not stated in the main publication, and the primary outcome stated by the author in an email and the secondary publication were different, so we rated this trial at high risk of bias (Thorleifsdottir 2012).

Other potential sources of bias

None identified.

Effects of interventions

See: **Summary of findings for the main comparison** Penicillin compared to no treatment for guttate psoriasis; **Summary of findings 2** Erythromycin compared to no treatment for guttate psoriasis; **Summary of findings 3** Azithromycin compared to vitamin C for chronic plaque psoriasis; **Summary of findings 4** Rifampicin compared to placebo for guttate psoriasis; **Summary of findings 5** Tonsillectomy compared to no intervention for chronic plaque psoriasis

We could not pool any data in this review because of heterogeneity of:

- intervention: different class of antibiotics: penicillin (Caca-Biljanovska 2002; Dogan 2008), macrolides – erythromycin (Dogan 2008), and azithromycin (Saxena 2010), and rifampicin Vincent 1992); or surgery (Thorleifsdottir 2012);
- comparator: no treatment (Caca-Biljanovska 2002; Dogan 2008; Thorleifsdottir 2012;), vitamin C (Saxena 2010), or placebo (Vincent 1992); and
- participants: plaques psoriasis (Saxena 2010; Thorleifsdottir 2012), or guttate psoriasis (Caca-Biljanovska 2002; Dogan 2008; Vincent 1992).

(1) Penicillin versus no treatment

(Summary of findings for the main comparison)

Two trials compared penicillin (penicillin 1.6 MU (million units) intramuscularly once daily for 14 days (Caca-Biljanovska 2002), and oral benzathine phenoxymethylpenicillin (penicillin V) 50,000 UI/kg/d for 14 days (Dogan 2008)) to no treatment in guttate psoriasis.

In Caca-Biljanovska 2002, participants of both groups received a co-intervention of ultraviolet B (UVB) and betamethasone.

Primary outcomes

1. Time-to-resolution (time between inclusion and resolution), where resolution was defined as participants achieving clear or almost clear skin (Physician Global Assessment (PGA) 0 or 1, or Psoriasis Area and Severity Index (PASI) 90 or 100)

This outcome was not reported.

2. Proportion of participants with adverse effects and severe adverse effects

In one trial, no adverse events were observed in either group (Caca-Biljanovska 2002).

In the other trial, adverse events were not reported (Dogan 2008).

Secondary outcomes

1. Proportion of participants achieving clear or almost clear skin (PGA 0 or 1 or PASI 90 or 100)

In Caca-Biljanovska 2002, there were six events of clearance in the penicillin group, and three events in the no treatment group at six weeks. There was no statistically significant difference between the two groups (relative risk (RR) 2.00, 95% confidence interval (CI) 0.68 to 5.85; 20 participants; Analysis 1.1).

The proportion of participants achieving clear or almost clear skin was not reported in the other trial (Dogan 2008). No difference was observed for mean PASI score between baseline and six weeks in each group (Dogan 2008).

2. Proportion of participants achieving PASI 75 or PGA 1 to 2

Results were reported as mean PASI score at baseline and at six weeks in both trials, and not as proportion of participants achieving PASI 75 or PGA 1 to 2. No difference was found between groups for mean PASI at six weeks in both trials (Caca-Biljanovska 2002; Dogan 2008).

3. Risk of having at least one relapse at long-term follow-up

Long-term follow-up was not reported.

(2) Erythromycin versus no treatment

(Summary of findings 2)

One trial compared oral erythromycin 1 g per day for 14 days to no treatment, in guttate psoriasis (Dogan 2008)

Primary outcomes

1. Time-to-resolution (time between inclusion and resolution), where resolution was defined as participants achieving clear or almost clear skin (Physician Global Assessment (PGA) 0 or 1, or Psoriasis Area and Severity Index (PASI) 90 or 100)

This outcome was not reported.

2. Proportion of participants with adverse effects and severe adverse effects

Adverse events were not reported.

Secondary outcomes

1. Proportion of participants achieving clear or almost clear skin (PGA 0 or 1, or PASI 90 or 100)

This outcome was not reported.

2. Proportion of participants achieving PASI 75 or PGA 1 to 2

Results were reported as a mean PASI score at baseline and at six weeks, and not as proportion of participants achieving PASI 75 or PGA 1 to 2. No difference was found between groups for mean PASI at six weeks (Dogan 2008).

3. Risk of having at least one relapse at long-term follow-up

Long-term follow-up was not reported.

(3) Azithromycin versus vitamin C

(Summary of findings 3)

One trial compared oral azithromycin 500 mg/d for four consecutive days every 14 days over 48 weeks in participants with chronic plaque psoriasis (Saxena 2010).

Primary outcomes

1. Time-to-resolution (time between inclusion and resolution), where resolution was defined as participants achieving clear or almost clear skin (Physician Global Assessment (PGA) 0 or 1, or Psoriasis Area and Severity Index (PASI) 90 or 100)

This outcome was not reported.

2. Proportion of participants with adverse effects and severe adverse effects

Adverse events (nausea and mild abdominal upset) were reported in 10/30 in the azithromycin group. There was no mention of the presence or absence of adverse events in the Vitamin C group.

Secondary outcomes

1. Proportion of participants achieving clear or almost clear skin (PGA 0 or 1 or PASI 90 or 100)

This outcome was not reported.

2. Proportion of participants achieving PASI 75 or PGA 1 to 2

At 48 weeks, 60% (18/30) of participants in the azithromycin group versus 0/20 in the vitamin C group reached PASI 75 (RR 25.06, 95% CI 1.60 to 393.59; 50 participants; Analysis 2.1).

3. Risk of having at least one relapse at long-term follow-up

This outcome was not reported.

(4) Rifampicin versus placebo

(Summary of findings 4)

One trial compared oral rifampicin 600 mg/d versus placebo for five days in participants with guttate psoriasis (Vincent 1992). participants of both groups received oral penicillin V 50,000 IU/kg/d or oral erythromycin 1 g/d for 14 days as a co-intervention.

Primary outcomes

1. Time-to-resolution (time between inclusion and resolution), where resolution was defined as participants achieving clear or almost clear skin (Physician Global Assessment (PGA) 0 or 1, or Psoriasis Area and Severity Index (PASI) 90 or 100)

This outcome was not reported.

2. Proportion of participants with adverse effects and severe adverse effects

Adverse events were not reported.

Secondary outcomes

1. Proportion of participants achieving clear or almost clear skin (PGA 0 or 1 or PASI 90 or 100)

This outcome was not reported. However, no change in psoriasis severity was observed in either group at 14 days and six weeks.

2. Proportion of participants achieving PASI 75 or PGA 1 to 2

This outcome was not reported.

3. Risk of having at least one relapse at long-term follow-up

Long-term follow-up was not reported.

(5) Penicillin versus erythromycin

One trial compared oral benzathine phenoxymethylpenicillin (penicillin V) 50,000 IU/kg/d to oral erythromycin 1 gr/d for 14 days in guttate psoriasis (Dogan 2008).

Primary outcomes

1. Time-to-resolution (time between inclusion and resolution), where resolution was defined as participants achieving clear or almost clear skin (Physician Global Assessment (PGA) 0 or 1, or Psoriasis Area and Severity Index (PASI) 90 or 100)

This outcome was not reported.

2. Proportion of participants with adverse effects and severe adverse effects

Adverse events were not reported.

Secondary outcomes

1. Proportion of participants achieving clear or almost clear skin (PGA 0 or 1 or PASI 90 or 100)

This outcome was not reported.

2. Proportion of participants achieving PASI 75 or PGA 1 to 2

Results were reported as mean PASI scores at baseline and at six weeks, and not as the proportion of participants achieving PASI 75 or PGA 1 to 2. No difference was found between groups for mean PASI at six weeks (Dogan 2008).

3. Risk of having at least one relapse at long-term follow-up

Long-term follow-up was not reported.

(6) Tonsillectomy versus no treatment

(Summary of findings 5)

One trial compared tonsillectomy to no treatment in participants with chronic plaque psoriasis (Thorleifsdottir 2012). Other treatments (topical or systemic) for psoriasis were allowed during the trial.

Primary outcomes

1. Time-to-resolution (time between inclusion and resolution) where resolution was defined as participants achieving clear or almost clear skin (Physician Global Assessment (PGA) 0 or 1 or Psoriasis Area and Severity Index (PASI) 90 or 100)

This outcome was not reported.

2. Proportion of participants with adverse effects and severe adverse effects

One participant had an adverse event (minor bleeding) in the tonsillectomy group (RR 2.81, 95% CI 0.12 to 63.83; 29 participants; Analysis 3.1).

Secondary outcomes

1. Proportion of participants achieving clear or almost clear skin (PGA 0 or 1 or PASI 90 or 100)

In the tonsillectomy arm, 1/15 (7%) participants achieved PASI 90 after eight weeks; there were none in the no intervention arm (RR 2.81, 95% CI 0.12 to 63.83; 29 participants; Analysis 3.2).

2. Proportion of participants achieving PASI 75 or PGA 1 to 2

Three of fifteen (20%) participants in the tonsillectomy group, and none in the no treatment group achieved PASI 75 after eight weeks (RR 6.56, 95% CI 0.37 to 116.70; 29 participants; Analysis 3.3).

3. Risk of having at least one relapse at long-term follow-up

Authors reported that five participants in the tonsillectomy arm had a recurrence of psoriasis lesions in the winter, without providing any more precise information.

DISCUSSION

Summary of main results

We included five trials: four assessed antibiotic treatment (penicillin, a macrolide (either erythromycin or azithromycin), or rifampicin). Three examined participants with guttate psoriasis (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 4); and one included participants with chronic plaque psoriasis (Summary of findings 3). One trial assessed the effects of tonsillectomy in participants with chronic plaque psoriasis (Summary of findings 5).

We performed no meta-analyses due to heterogeneity of participants' characteristics (guttate or plaque psoriasis) and interventions. No studies reported our efficacy primary outcome of time-to-resolution (time between inclusion and resolution), where resolution was defined as participants achieving clear or almost clear skin (Physician Global Assessment (PGA) 0 or 1, or Psoriasis Area and Severity Index (PASI) 90 or 100. None of the studies measured the risk of having at least one relapse at long-term follow-up, either.

We rated the certainty of evidence as very low for all reported outcomes, because the five included trials were at high risk of bias, the results were imprecise, and the trials involved a small number of participants, with almost no children. Therefore, we are uncertain of the accuracy of the results that we report, and the efficacy and safety of antistreptococcal interventions.

Adverse events were not measured in the two trials that compared rifampicin against placebo, and erythromycin or penicillin against no treatment. In the three remaining trials, adverse events were reported in those taking azithromycin (nausea and mild abdominal upset), but there was no information provided about adverse events in those given vitamin C (50 participants randomised, measured at 48 weeks); there was only one minor adverse event (minor bleeding) reported in participants who had a tonsillectomy, and none reported in those given no treatment (29 participants randomised, measured at eight weeks); and in the trial comparing penicillin with no treatment, no adverse events were seen in either group (20 participants randomised, measured at six weeks).

The proportion of participants achieving clear or almost clear skin (Physician Global Assessment (PGA) 0 or 1, or Psoriasis Area and Severity Index (PASI) 90 or 100) was only reported in one trial on guttate psoriasis, in which penicillin was compared to no treatment (20 participants randomised). We are uncertain if the number of participants with guttate psoriasis achieving clear or almost clear skin differed between groups at six weeks. Similarly, PASI 90 was measured in only one chronic plaque psoriasis trial, which compared tonsillectomy with no intervention (29 participants randomised): only one participant in the tonsillectomy group achieved PASI 90, measured after eight weeks. Three trials, which compared rifampicin with placebo, erythromycin or penicillin with no treatment, and azithromycin with vitamin C, did not measure this outcome.

The proportion of participants achieving PASI 75 or PGA 1 to 2 was not measured in any guttate psoriasis trial, so there were no results for rifampicin versus placebo, and penicillin or erythromycin versus no treatment. However, the number of participants reaching PASI 75 was measured in both chronic plaque psoriasis trials. PASI 75 was achieved at 48 weeks in just over half of the participants (18/30) in the azithromycin group versus none in the group taking vitamin C (50 participants randomised). Three out of 15 participants in the tonsillectomy group achieved PASI 75 compared with none in the no treatment group after eight weeks (29 participants randomised).

Overall completeness and applicability of evidence

The evidence is incomplete for antistreptococcal interventions for guttate psoriasis. We found three trials assessing systemic antibiotic treatment in 83 participants with guttate psoriasis.

The objective of treatment is to shorten the time-to-resolution of guttate psoriasis, and to reduce the number of people with long-term chronic plaque psoriasis. Thus, we considered time-to-resolution as a primary outcome of interest for efficacy, where resolution was defined as participants achieving clear or almost clear skin within eight weeks of the start of treatment. This outcome was not assessed or reported in the three guttate psoriasis trials. We also considered the risk of having at least one relapse at long-term

follow-up as an outcome of interest. It was not reported in any of the three trials, which lasted only six to eight weeks. Adverse events were not reported at all in two trials, and very briefly described in the third.

The evidence is also incomplete for antistreptococcal interventions for chronic plaque psoriasis. We found two trials involving 79 participants; one assessed long-term antibiotic treatment (azithromycin for 48 weeks from baseline), and one trial assessed the effects of tonsillectomy. They did not report on time-to-resolution, or risk of at least one relapse at long-term follow-up. One trial reported on adverse events in the treated group only, the other trial very briefly described adverse events.

The mean age of the participants was 26 years (a minimum age of 12 years to a maximum of 77 years); only two participants were under 15 years old, yet guttate psoriasis is described as more frequent in children and young adults (Mercy 2013). The included population was heterogeneous in term of severity; participants had mild to severe psoriasis, as attested by baseline PASI scores.

More men than women were included (100 men/62 women). Future trials should try to recruit equally from both sexes, since the burden of psoriasis is shared roughly equally by both sexes (GHDx 2018).

The link between proven infection and effect of antistreptococcal treatment was something we hoped to investigate via subgroup analyses, regarding the presence, absence, or unknown status of active *Streptococcal* infection at the time of treatment onset, but it was not possible, due to our inability to meta-analyse. However, we noted that in the three trials concerning guttate psoriasis, only 10% of the participants were found to have a positive throat swab culture. The baseline results for culture of swab were reported as equivocal in one trial on chronic plaque psoriasis, and only half of participants in both groups were colonised by *Streptococci* in the other. In total, *Streptococcus* bacteria were found in the throats of only 23 people (about 14%).

The choice of antibiotic is questionable, as two comparisons assessed penicillin, and two comparisons assessed rifampicin and erythromycin, while current guidelines recommend using penicillin V or amoxicillin to treat *Streptococcal* pharyngitis (Shulman 2012). Amoxicillin was not assessed by any of the included studies.

Quality of the evidence

The results for all outcomes measured in this review were based on very low-certainty evidence.

We downgraded the evidence, and rated it as very low for the three comparisons reporting at least one of our outcomes. There was a high or unclear risk of bias in the included studies for:

- blinding of participants, caregivers, or assessors;
- selective outcome reporting (no primary outcome specified);
- incomplete outcome data.

We also downgraded the evidence for imprecision for all comparisons, because the included studies had a small number of participants, which resulted in wide confidence intervals.

The small number of included studies and heterogeneity of participants and interventions did not allow assessment of publication bias, or meta-analysis.

Potential biases in the review process

We attempted to conduct a comprehensive search for studies, but we did not succeed in obtaining results of a study comparing Bicillin LA to placebo, which was registered in 2007, and listed as terminated because there were not enough enrollees to obtain a valid conclusion (NCT00427609). When there were missing data from results, or information that prevented us from assessing risk of bias, we contacted the authors of those trials to request additional information; however, we did not receive any reply from several trialists.

We found a trial comparing a topical antibiotic (polymyxin B) to vehicle in plaque psoriasis (Stutz 1996). We decided not to include this study, because it was not in line with the physiopathological hypothesis linking infection and psoriasis. As finding a trial assessing a topical antibiotic was not anticipated, the protocol did not specify initially that only systemic antibiotics were considered. We added this point in the section Differences between protocol and review.

Agreements and disagreements with other studies or reviews

The previous version of this Cochrane Review assessed the same question, concluding that no evidence was available about the efficacy of antistreptococcal intervention in cutaneous psoriasis (Owen 2000). They included only one trial, which was also included in this review (Vincent 1992). We included four additional trials, published after 2000. Our conclusion was different from the conclusion of the systematic review Rachakonda 2015, which concluded that "tonsillectomy may be a potential option for people with recalcitrant psoriasis associated with episodes of tonsillitis". Rachakonda 2015 considered including all types of study designs (clinical cases to randomised controlled trials) that assessed the efficacy of tonsillectomy, and included one randomised controlled trial, also included in our review (Thorleifsdottir 2012); one retrospective study; four prospective observational studies; seven case reports; and seven case series. They did not perform a formal assessment of risk of bias.

The antibiotics assessed by the studies in our review are not in accordance with national recommendations (Shulman 2012). Furthermore, the indication for tonsillectomy does not aline with current guidelines that do not recommend tonsillectomy solely to reduce the frequency of *Group A Streptococcal* pharyngitis (Shulman 2012).

AUTHORS' CONCLUSIONS

Implications for practice

We do not have sufficient evidence to determine the effects of antistreptococcal interventions for guttate and chronic plaque psoriasis. The evidence we found for systemic antibiotic treatment in participants with guttate psoriasis, and for systemic antibiotic treatment and tonsillectomy in participants with chronic plaque psoriasis, was of very low quality. Thus, we cannot be certain of the accuracy of the results found.

The one study awaiting classification may alter the conclusions of the review once assessed.

A number of our outcomes of interest were either not addressed, or were addressed inadequately. The study populations were small in number, and not reflective of those with guttate psoriasis or chronic plaque psoriasis. We could only include a small number of trials and those we did include, were at high or unclear risk of bias for reasons, such as lack of blinding and outcome reporting issues. The treatments assessed did not include those regarded in the literature as important, and finally, our included studies did not facilitate investigation of active *Streptococcal* infection at the time of treatment.

Implications for research

A relationship between *Streptococcal* infection and guttate psoriasis onset is suspected, although it is not based on high-quality evidence.

Further, well-designed, randomised trials assessing antibiotic treatment are needed for guttate psoriasis, and we suggest the following PICO.

Participants

Guttate psoriasis is more prevalent in young adults and children, so this population should be included in future trials of guttate psoriasis. Inclusion criteria should include *Streptococcal* infection, diagnosed by swabbing the throat and testing for *Group A Streptococcal* (GAS) pharyngitis, using a rapid antigen detection test (RADT), culture, or both. There is a need for validated tools to assess the severity of guttate psoriasis in children and young adults.

Intervention

Penicillin V or amoxicillin, according to recommendations for the treatment of *Streptococcal* pharyngitis.

Comparator

Options for the comparator include topical steroids, a combination of topical steroids and vitamin D analogues, or phototherapy, and placebo.

Outcomes

In the absence of a core outcome set available for guttate psoriasis, we suggest four important outcomes. The most relevant primary outcome for a form of psoriasis that resolves in a few weeks is time-to-resolution (time between inclusion and resolution), where resolution is defined as participants achieving clear or almost clear skin. Long-term follow-up (one year) of the rate of developing a chronic form of psoriasis is another important outcome, since preventing chronic psoriasis is a goal of treatment. Quality of life and adverse effects should also be included as outcomes.

To avoid high risk of bias, design of these future trials should ensure blinding of participants, personnel, and outcome assessors, as outcomes are subjective. To avoid imprecision, future studies should include a sample size calculation to ensure the study is adequately powered. They should also ensure they follow the CONSORT guideline for clinical trials, to improve the quality of research, reducing risk of bias, and guide decision making (Moher 2010).

More evidence on the relationship between flares of chronic plaque psoriasis and infection is needed prior to further interventional trials assessing antistreptococcal intervention in this form of psoriasis.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Caca-Biljanovska 2002

Methods	Randomised, open-label, parallel group, controlled trial One centre in Macedonia Period of inclusion: February 2000 to January 2002
Participants	**Inclusion criteria:** • Age ≥ 18 years • Histologically confirmed guttate psoriasis • Normal results of physical and biochemical tests (serum albumin, lipids, total calcium, albumin-adjusted total calcium, urea, phosphate, alkaline phosphatase, and creatinine) **Exclusion criteria:**

Caca-Biljanovska 2002 *(Continued)*

- Use of phototoxic or immunosuppressive drugs
- Presence of other skin lesions (actinic keratoses or lentigo) or photodamaged skin
- Use of systemic or intralesional therapy or photo(chemo)therapy for psoriasis in the previous two months
- Use of topical treatments during the study period
- Conditions or medications that might interfere with, or sensitise people to any of the treatments
- Concomitant bacterial, fungal, or viral skin infections
- Significant worsening of the clinical state during the therapy, development of serious adverse effects, or both
- Nonadherence to the treatment

Baseline data:

Randomised: penicillin (N = 10), no treatment (N = 10)

- Age (median (range)), years: penicillin 22 (16 to 32); no treatment 25 (17 to 37)
- Male/female: 9/11
- Duration of conditions, days (median; (range)): penicillin 25 (19 to 45); no treatment 22 (15 to 35)
- Chronic plaque psoriasis (n): 0
- Guttate psoriasis (n): 20
- PASI score (mean; SD): penicillin 5.7 ± 2.1; no treatment 5.9 ± 2.5
- Number of participants with positive culture of nose and throat swabs: none in either group

Withdrawal: information not available

Interventions	**Duration of period of treatment:** 6 weeks **Follow-up after treatment:** 2 weeks Intervention 1: penicillin 1.6 10^6u, IM once a day for two weeks Intervention 2: none Co-intervention 1: topical therapy with betamethasone dipropionate 0.05% cream, once daily after the phototherapy Co-intervention 2: phototherapy 4 times a week over 6 weeks The two co-interventions were given to all participants in both groups
Outcomes	Primary outcome: not stated At 6 weeks, change in clinical condition in comparison with baseline: "0 = worse; 1 = no change; 2 = moderate improvement (partial reduction in scaling, erythema, infiltration, or some combination); 3 = considerable improvement (significant reduction in all three variables); and 4 = clearing" PASI was assessed after 2, 4, 6, and 8 weeks of treatment
Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly allocated by ClinStat software (www.sghms.ac.uk/depts/phs/staff/jmb/jmbsoft.htm)" Comment: random sequence generation performed by computer with a suitable software

Caca-Biljanovska 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label" Comment: the trial was described as open-label by the authors; participants and personnel were not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label" Comment: the trial was described as open-label by the authors; outcome assessors were not blinded and the outcomes were subjective
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of randomly assigned participants: 20 Number of analysed participants: 20 Comment: there was no information on missing data and how they were handled
Selective reporting (reporting bias)	Unclear risk	Comment: no primary outcome stated, protocol not available; no protocol found in clinical registries

Dogan 2008

Methods	Randomised, single-blind, parallel group, controlled trial One centre; Istanbul,Turkey Period of inclusion: 2001 to 2005
Participants	**Inclusion criteria:** • Guttate psoriasis based on physician assessment • Cultural, serologic evidence, or both, of β-haemolytic *Streptococcal* colonization: > 200 UI/mL, or positive serology **Exclusion criteria:** • Antibiotics for any purpose in the past 30 days **During the treatment and follow-up period** • Other topical and systemic treatments including phototherapy were not allowed, except topical emollients in all groups **Baseline data:** Randomised: erythromycin (N = 14), phenoxymethylpenicillin (N = 14), no treatment (N = 15) • Age (Mean; extremes), years: 21 (19 to 23) • Male/female: 43/0 • Duration of conditions (years): not stated, "at least 6 months" • Guttate psoriasis (n): 43 • Pasi score (mean): erythromycin 12.2, phenoxymethylpenicillin 11.1, no treatment 11.1 • Number of participants with positive throat swab culture (streptococcus): 8 **Withdrawal:** information not available
Interventions	**Duration of period treatment:** 14 days

Dogan 2008 *(Continued)*

	Follow-up after treatment: 4 weeks Intervention 1: no treatment Intervention 2: oral erythromycin 250 mg 4 times a day Intervention 3: oral benzathine phenoxymethylpenicillin 50 000 IU/kg/d, in 3 doses Co-intervention(s): none During the treatment and follow-up period: no topical and systemic treatments, including phototherapy
Outcomes	Primary outcome: not stated Mean PASI scores 14 d (end of treatment) and 6 weeks (once in 2 weeks with PASI scores)
Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: method used to generate the allocation sequence was not reported
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "PASI scorings were performed by the same physician, who was blind to the groups, before and after the treatment" Comment: no double dummy; one no treatment group, hospitalised participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "PASI scorings were performed by the same physician, who was blind to the groups, before and after the treatment" Comment: hospitalised patients; no description of measures taken to guarantee no communication between caregivers, participants, and assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of randomly assigned participants: 43 Comment: the number of analysed participants is uncertain, and there is no information on missing data and how they were handled
Selective reporting (reporting bias)	Unclear risk	Comment: no primary or secondary outcome stated in the methods section; no registration of the trial was found

Saxena 2010

Methods	Randomised, single-blind, parallel group, controlled trial Two centres in Jaipur, India Period of inclusion: not stated
Participants	**Inclusion criteria:**

Saxena 2010 *(Continued)*

- Histologically confirmed moderate to severe chronic plaque psoriasis

Exclusion criteria:

- Pustular psoriasis
- History of spontaneous remission of the disease
- Pregnancy
- Other associated systemic diseases, specifically with hepatic involvement

During the treatment and follow-up period:

- participants taking any prior treatment were advised to discontinue it for two weeks before they were enrolled in this trial
- Routine blood counts, ASLO titre, C-reactive protein, throat swab cultures, blood sugar, blood urea, creatinine, and liver function tests were done

Baseline data

Randomised: azithromycin (N = 30), vitamin C tablets (N = 20);

Analysed: azithromycin (28), vitamin C tablets (15)

- Mean age (extremes), years: mean not stated "(13 years to 63 years)"
- Male/female: 32/18
- Duration of conditions, (years): not stated
- Chronic plaque psoriasis (n): 50
- PASI score (mean): azithromycin 27 (N = 28), vitamin C tablets 19 (N = 15)
- Number of participants with positive culture of throat swabs: results not presented; quote: "Equivocal results"

Withdraw: azithromycin (n = 2, one at 24 weeks, and one at 36 weeks), vitamin C tablets (n = 5)

Interventions	**Duration of period treatment:** 48 weeks **Follow-up after treatment:** 0 weeks Intervention 1: oral azithromycin 500 mg once a day for 4 days, with a gap of 10 days (total of 24 such courses) Intervention 2: vitamin C tablets, the same dosage, form Co-intervention: none
Outcomes	**Primary outcome:** not stated "The disease severity was evaluated using a clinical scoring system i.e. a system translating a clinical judgement into a scale – the Psoriasis Area and Severity Index (PASI). Based on PASI score, clinical assessments of redness, scaling, and thickness of lesions were done in all the participants and response to treatment was graded as nil (< 10%), mild (11 to 30%), moderate (31 to 60%), good (61 to 90%), and excellent (91 to 100%) improvement" **Time to evaluate:** at 12-week intervals, up to 48 weeks from baseline
Notes	Funding: "Financial support: none"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly allocated"

Saxena 2010 *(Continued)*

		Comment: no description on the method used; 30 versus 20 randomised participants per group
Allocation concealment (selection bias)	Unclear risk	Comment: no centralised randomisation, information, and treatment with distinct appearance
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "single-blind" "our patients neither guessed nor enquired about the tablet, as only chewable forms of Vitamin C 500 mg are routinely prescribed and/or available" Comment: not really a placebo but vitamin C, and it is probable that the taste is recognisable The trial is described as single-blind, however, it was not clearly explained who was supposed to be blinded, participant or assessor
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "single-blind" "The patients were crossed for scoring, and the same patient was always scored by the same clinician" Comment: The trial is described as single-blind, however, it was not clearly explained who was supposed to be blinded, participant or assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of randomly assigned participants: 50 (30 to 20) Number of analysed participants: azithromycin 29, vitamin C 15 Number of lost to follow-up: unbalanced between groups and reason not stated azithromycin 2, vitamin C 5 Comment: 25% of randomised participants were lost to follow-up in the vitamin C group; no reasons were provided
Selective reporting (reporting bias)	Unclear risk	Comment: no primary outcome presented in the method; trial not found in clinical registries

Thorleifsdottir 2012

Methods	Randomised, single-blind, parallel group, controlled trial Number of centres: 1 centre in Reykjavik, Iceland Period of inclusion: not stated
Participants	**Inclusion criteria:** • ≥ 18 years of age • Chronic plaque psoriasis diagnosed by a dermatologist • History of psoriasis exacerbation during or shortly after throat infections **Exclusion criteria:** • Heart and lung diseases **During the treatment and follow-up period:** • The participants were off treatment, including antibiotics, for at least 4 weeks before they entered the study, and for 2 months thereafter. Subsequently, the participants were allowed to have treatment according to what they and their dermatologists thought was indicated.

Thorleifsdottir 2012 *(Continued)*

	Baseline data: Randomised: tonsillectomy (N = 15); no treatment (N = 14) • Age, years (mean): 35, 36 • Male/female: 9/20 • Duration of conditions, years (mean): 20, 20 • Chronic plaque psoriasis (n): 29 • PASI score (mean; SD): tonsillectomy 11; no treatment 9.3 At baseline: 8/15 of the TX Group were colonised by *Streptococci* and 6/14 of the controls (additional information provided by the author by email) **Withdraw:** none
Interventions	**Duration of period treatment:** surgical intervention **Follow-up after treatment:** 2 years Intervention 1: tonsillectomy Intervention 2: no treatment The participants were off treatment, including antibiotics, for at least 4 wk before they entered the study and for 2 months thereafter; participants could have anti-psoriasis treatment during follow-up if needed
Outcomes	**Primary outcome:** not stated in primary publication, complementary information provided by the author by email when requested: • Reduction of the PASI and a coinciding decrease in the blood frequency of T lymphocytes that recognise auto-antigens in the skin **Secondary outcomes:** • The change in validated health-related quality of life scores; PDI and PLSI, at 12 and 24 months • Correlation between the change in clinical status (PASI) and health-related quality of life scores (PDI and PLSI) • Proportion of participants who achieve ≥ 50% reduction in PASI from baseline (PASI 50) • Proportion of participants who achieve PASI 75 and PASI 90 (follow-up at 8 weeks) • Changes in serum concentrations of cytokines after tonsillectomy • Genetic and clinical profile that predicts best response to tonsillectomy **Primary outcome stated in a secondary publication**: primary endpoints were defined as clinically significant changes in quality of life, assessed by PDI (and PLSI) at 12 and 24 months
Notes	Funding: the Icelandic Research Fund, the Icelandic Research Fund for Graduate Students, the University of Iceland Research Fund, and the Science Fund of the National University Hospital in Iceland.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "simple randomisation in a 1:1 ratio. A numerical code was used to identify patients and their specimens" Comment: information provided by author after email contact
Allocation concealment (selection bias)	Unclear risk	Quote: "The study's supervisor was responsible for the randomisation and only he had access to the numerical code."

Thorleifsdottir 2012 *(Continued)*

		Comment: It is not clear if supervisor was aware of the group of randomisation of next participant
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participant not blinded (surgery versus no intervention)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The clinical evaluation was observer-blinded with regard to tonsillectomy". "All included patients had strict instructions not to reveal their tonsil status to the investigator who did all the assessments." Comment: information provided by author after email contact information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of randomly assigned participants: 29 Number of analysed participants: control: 14, tonsillectomy: 15 Number lost to follow-up: 0 Comment: it was clearly specified that no participant was lost to follow-up; all participants randomised were included in the analysis
Selective reporting (reporting bias)	High risk	Comment: No primary or secondary outcomes stated in the methods section of the published report. Primary outcome stated by the authors (through mail upon request) was different from primary outcome stated in a secondary publication.

Vincent 1992

Methods	Randomised, placebo, parallel group, controlled trial Number of centres and country: not stated Period of inclusion: November 1987 to June 1989
Participants	**Inclusion criteria:** • Guttate psoriasis, psoriasis in a person with a recent history of upper respiratory tract infection, inverse psoriasis, or recalcitrant psoriasis • Cultural or serologic evidence of β-haemolytic *Streptococcal* colonisation **Exclusion criteria:** • Antibiotic recently **During the treatment and follow-up period:** • During the study all other treatment for psoriasis was stopped, except for topical emollients **Baseline data:** Randomised: oral rifampicin (N = 9), placebo (N = 11) • Age, mean (extremes), years: 35 (12 to 77) • Male/female: 7/13 • Guttate psoriasis (n): 19 • Recalcitrant psoriasis (n): 1 • Number of participants with positive culture (β-haemolytic*streptococcus*) of throat swabs: n = 1

Vincent 1992 *(Continued)*

Interventions	**Duration of period treatment:** 14 days **Follow-up after treatment:** 4 weeks Intervention 1: oral rifampicin 300 mg twice daily for 5 days (d 10 to 14) Intervention 2: placebo twice daily for 5 days (d 10 to 14) Co-intervention: Penicillin V or erythromycin 250 mg four times a day for 14 days
Outcomes	**Primary outcome:** Not stated "PASI method at 3 and 6 weeks after the treatment, and repeat culture and *Streptococcal* serologic tests were done"
Notes	Funding: Merell Dow Co (Pharmaceuticals)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated" Comment: method used to generate the allocation sequence was not reported
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the method used to guarantee allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no description about blinding, but rifampicin produces red urine
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no description about blinding, but it was possible to obtain from information on the colour of the participant's urine
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of randomly assigned participants: N = 20 Number of analysed participants: not stated Number lost to follow-up: no information Comment: no information provided on number lost to follow-up, and number of participants analysed
Selective reporting (reporting bias)	High risk	Comment: primary outcome not stated Outcomes presented in the protocol were not reported in the results; trial not found in clinical registries

PASI: Psoriasis area and severity index
d: day
PDI: Psoriasis Disability Index
PLSI: Psoriasis Life Stress Inventory
ASLO: anti-streptolysin O antibody

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Falagas 2008	Systematic review and meta-analysis
Forstrom 1974	Not controlled
Gudjonsson 2003	No intervention, not randomised
Komine 2000	Not randomised
Kurwa 1973	Not randomised
Masood 1997	Only able to obtain abstract. We assumed this study was uncontrolled. The authors claimed that in 200 unselected psoriasis participants treated with phenoxymethylpenicillin, excellent responses were observed in guttate psoriasis (80% complete clearance), good responses in acute exacerbation of chronic psoriasis (50% clearance), and poor in chronic plaque psoriasis (10% clearance).
Nyfors 1973	Not randomised
Owen 2001	Review
Rappersberger 1996	Other treatment (topical immunosuppressive treatment)
Raza 2007	Not randomised
Rosenberg 1986	Case control study
Stutz 1996	Topical antibiotic
Tsankov 2011	Not randomised; this trial compared rifampicin to placebo in participants with guttate psoriasis; in one intervention group, participants were *Streptococcus* positive, and in the second intervention group, *Streptococcus* negative. There were up to 82 participants in the intervention group and only 10 in the placebo group.

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00427609

Methods	Randomised controlled, double-blind Parallel assignment Location: University of Tennessee Health Science Center, Memphis, Tennessee, USA
Participants	• Male or female between 18 and 50 years of age (with onset before age 40) • Presence of chronic plaque type psoriasis unresponsive to treatment with topical preparations and extensive enough to consider appropriateness of systemic therapy • Guttate form of psoriasis • Non-responsive to treatment or worsening of the pre-existing psoriasis • With the exception of their skin disease, in good general state of health based on a complete medical history, blood test, and urine analysis • Females must have negative urine pregnancy test and willing to take additional measures to keep from becoming pregnant during the course of the study • No systemic prescription medication to control psoriasis within past 30 days • Free of any topical antipsoriatic preparation for the duration of the study, with the exception of emollients and moisturisers

NCT00427609 *(Continued)*

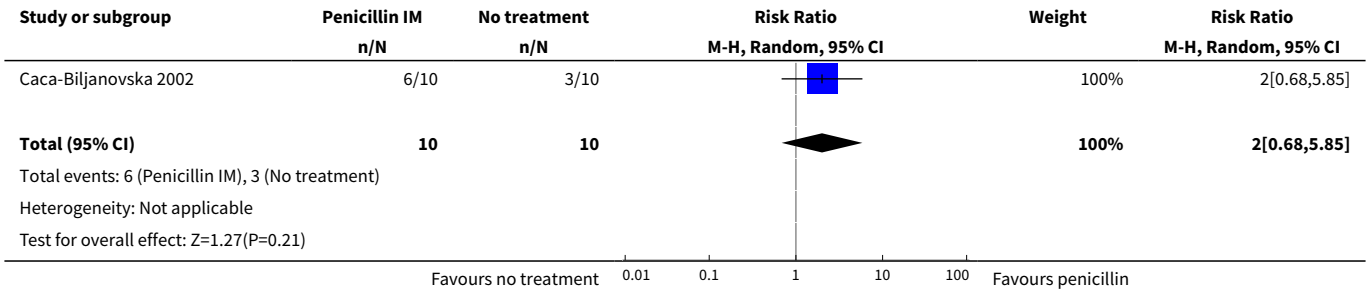
	Exclusion Criteria: • Pustular forms of psoriasis, either localised or generalised • Generalised erythrodermic psoriasis • Only palmoplantar psoriasis • Only scalp psoriasis • Only nail psoriasis • Only inverse psoriasis • Diabetes or impaired glucose tolerance • History of recurrent yeast infections • History of hypersensitivity to penicillin • History of severe adverse drug reactions • Pregnancy • Lactation • HIV/AIDS • History of renal disease • History of liver disease • History or presence of alcohol and/or drug dependence or abuse • History of significant psychiatric illness • History of allergy, asthma, allergic rhinitis, or urticaria • Subjects in other research trials at least 30 days prior to the beginning of this study
Interventions	Bicillin L-A administered intramuscularly in a dose of 2.4 million units every three weeks versus placebo The duration of intervention administration was not indicated
Outcomes	A reduction of an individual's PASI by 75% after five treatments of the active drug (Bicillin L-A). To demonstrate benefit comparable to the currently available biologicals, the response rate of Bicillin L-A must be at least 40% (time Frame: one year) No more precision on outcome time points
Notes	Unpublished trial: It was stated in 'recruitment status' that the trial was terminated (not enough enrollees to obtain a valid conclusion) on 21 April 2015

DATA AND ANALYSES

Comparison 1. Penicillin versus no treatment in guttate psoriasis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants achieving clear or almost clear skin (PASI 90 or 100 or PGA 0 or 1)	1	20	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.68, 5.85]

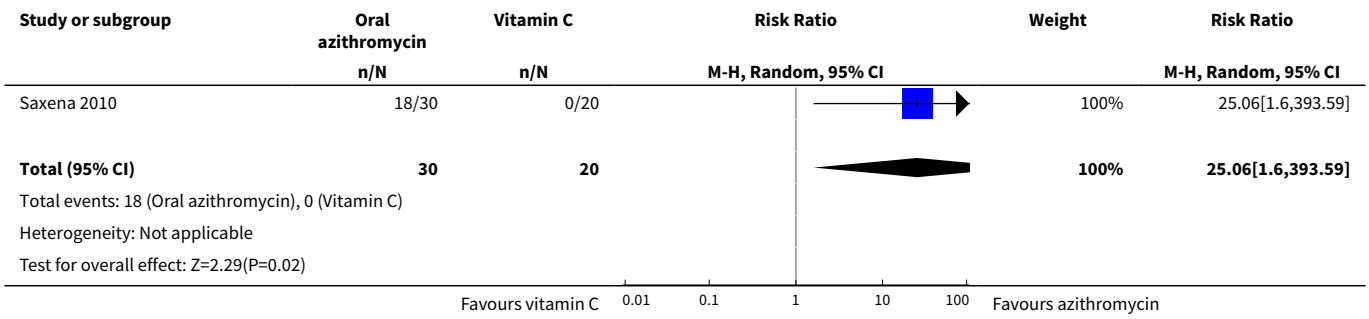
Analysis 1.1. Comparison 1 Penicillin versus no treatment in guttate psoriasis, Outcome 1 Proportion of participants achieving clear or almost clear skin (PASI 90 or 100 or PGA 0 or 1).



Comparison 2. Oral azithromycin versus vitamin C in chronic plaque psoriasis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants achieving PASI 75 or PGA 1 to 2	1	50	Risk Ratio (M-H, Random, 95% CI)	25.06 [1.60, 393.59]

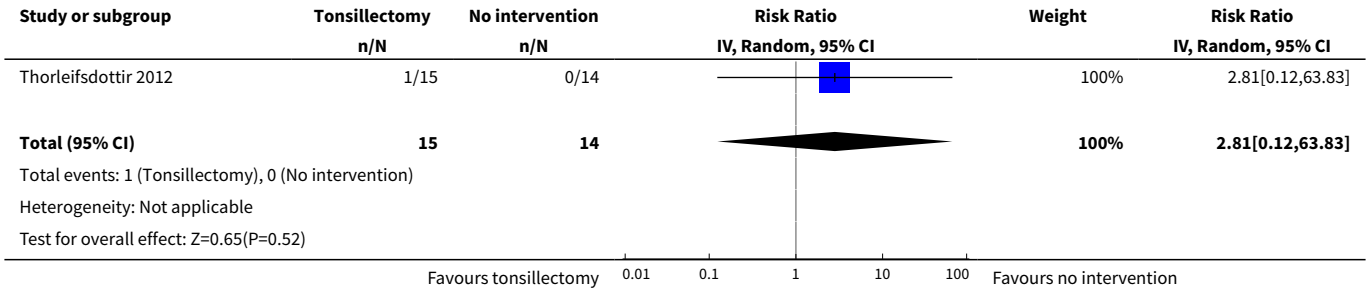
Analysis 2.1. Comparison 2 Oral azithromycin versus vitamin C in chronic plaque psoriasis, Outcome 1 Proportion of participants achieving PASI 75 or PGA 1 to 2.



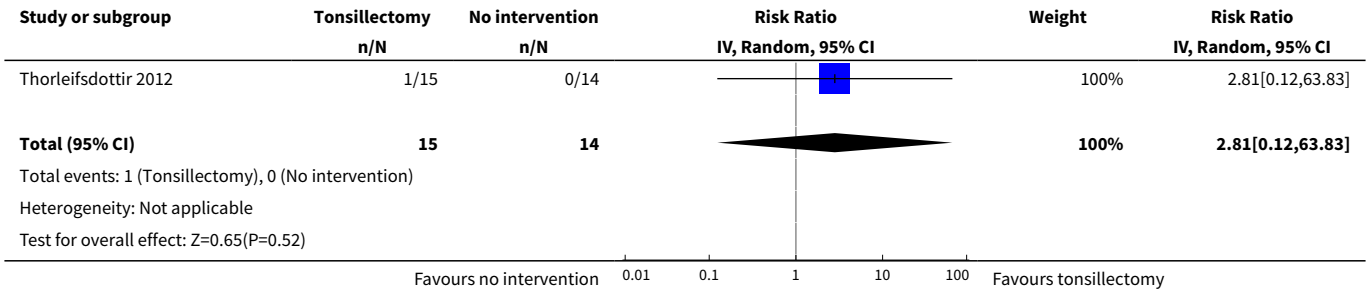
Comparison 3. Tonsillectomy versus no intervention in chronic plaque psoriasis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with adverse events or severe adverse events	1	29	Risk Ratio (IV, Random, 95% CI)	2.81 [0.12, 63.83]
2 Proportion of participants achieving clear or almost clear skin (PASI 90 or 100 or PGA 0 or 1)	1	29	Risk Ratio (IV, Random, 95% CI)	2.81 [0.12, 63.83]
3 Proportion of participants achieving PASI 75 or PGA 1 to 2	1	29	Risk Ratio (IV, Random, 95% CI)	6.56 [0.37, 116.70]

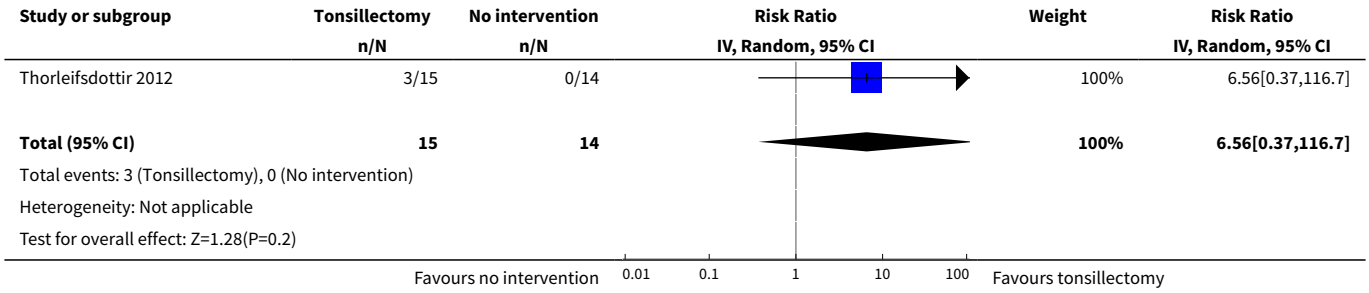
Analysis 3.1. Comparison 3 Tonsillectomy versus no intervention in chronic plaque psoriasis, Outcome 1 Number of participants with adverse events or severe adverse events.



Analysis 3.2. Comparison 3 Tonsillectomy versus no intervention in chronic plaque psoriasis, Outcome 2 Proportion of participants achieving clear or almost clear skin (PASI 90 or 100 or PGA 0 or 1).



Analysis 3.3. Comparison 3 Tonsillectomy versus no intervention in chronic plaque psoriasis, Outcome 3 Proportion of participants achieving PASI 75 or PGA 1 to 2.



ADDITIONAL TABLES

Table 1. Glossary of terms used

Term	Explanation
Acute pharyngitis	Inflammation of the mucous membrane of the pharynx; sore throat

Table 1. Glossary of terms used *(Continued)*

Adenotonsillectomy	Surgical removing of tonsils and adenoids
Anaphylactic shock	Allergic reaction characterised by swelling, collapse, and respiratory distress
Antistreptolysin O titre	Blood test to measure antibodies against streptolysin O, a substance produced by group A *Streptococcus* bacteria
Beta-haemolytic streptococcus	Pathogenic *Streptococci*, anaerobic bacteria, gram positive, often arranged in a chain
Chronic tonsillitis	Constant or recurrent infection of tonsils
Cytokines	Broad category of small proteins that are important in cell signalling. They are released by cells, and affect the behaviour of other cells and sometimes the releasing cell itself
Cutaneous lymphocyte–associated antigen (CLA)	The CLA is a fucose-containing carbohydrate that is attached to P-selectin glycoprotein ligand-1 on T cells. CLA is expressed on the surface of most T cells recovered from skin, and on about 5% to 10% of circulating CD8+ T cells
Dendritic cells	A subtype of white blood cells
Epidermal	Related to the outer layer of the skin
Epidermal hyperplasia	Abnormal increase in the number of normal cells in the epidermis of the skin, which increases its volume
Erythematous	Redness of the skin
Erythematosquamous	Redness and covered with scales
Hyperkeratosis	Thickening of the cornea
Histological	Related to the examination of a piece of tissue, with a microscope
Homozygous	Having identical pairs of genes for any given pair of hereditary characteristics
Heterozygous	Having dissimilar pairs of genes for any given pair of hereditary characteristics
Interleukin 17 (IL-17)	A pro-inflammatory cytokine
Immune-mediated disease	Group of conditions or diseases that lack a definitive etiology, but that are characterised by common inflammatory pathways leading to inflammation, and which may result from, or be triggered by, a dysregulation of the normal immune response
Keratinocytes	The most important cell type in the epidermis, the most superficial layer of the skin
Macrolide antibiotics	A specific family of antibiotics
Neutrophils	A subtype of white blood cells
Psoriasis Area Severity Index (PASI)	Index used to express the severity of psoriasis. It combines the severity (erythema or redness, induration, and desquamation) and percentage of the affected area
Physician Global Assessment (PGA)	Average assessment of all psoriatic lesions based on erythema (redness), scale, and induration
Pathogens	Micro-organisms responsible for infection (such as virus or bacteria)

Table 1. Glossary of terms used *(Continued)*

Pathophysiology, physiopathological	Convergence of pathology with physiology. Pathophysiology seeks to explain the physiological processes or mechanisms whereby a condition develops and progresses
Ribonucleic acid (RNA)	Polymeric molecule. It is involved in a range of biological roles in coding, decoding, regulation, and expression of genes
Serology/serologic	Refers to the diagnostic identification of antibodies in the serum
Stevens-Johnson syndrome	Allergic reaction to a drug characterised by mucous membrane and skin epidermal necrolysis and involving less than 10% of the entire body surface
Toxic epidermal necrolysis	Allergic reaction to a drug characterised by mucous membrane and skin epidermal necrolysis and involving more than 30% of the entire body surface
T lymphocytes, T cells	A subtype of a white blood cell

Table 2. Authors contact

Author	Date contacted	Reply
Dr Dogan (Dogan 2008)	6 October 2012; 17 October 2012	No answer
Dr Saxena (Saxena 2010)	29 March 2016; 18 April 2016	No answer
Dr V'lckova-Laskoska (Caca-Biljanovska 2002)	29 March 2016; 18 April 2016	No answer

Dr Vladimarsson (Thorleifsdottir 2012)	29 March 2016; 18 April 2016; 21 April 2016	**1. Did you have primary or secondary outcomes?**
		• Reply: the primary prespecified endpoints in the RCT were reduction of the Psoriasis Area and Severity Index (PASI) and a coinciding decrease in the blood frequency of T lymphocytes that recognise auto-antigens in the skin. These parameters, along with secondary outcome measures were compared to baseline values for each patient in the two groups.
		• The key secondary endpoints included:
		  • The change in validated health-related quality of life scores; the Psoriasis Disability Index (PDI) and Psoriasis Life Stress Inventory (PLSI) at 12 and 24 months
		  • Correlation between the change in clinical status (PASI) and health-related quality of life scores (PDI and PLSI)
		  • Proportion of patients who achieve ≥ 50% reduction in PASI from baseline (PASI 50)
		  • Proportion of participants who achieve PASI 75 and PASI 90
		  • Changes in serum concentrations of cytokines after tonsillectomy
		  • Genetic and clinical profile that predicts best response to tonsillectomy
		2. Could you give me more information concerning the results?
		• Time-to-resolution (time between inclusion and resolution), where resolution is defined as participants achieving clear or almost clear skin (Physician

Table 2. Authors contact *(Continued)*

Global Assessment (PGA) 0 or 1 or Psoriasis Area and Severity Index (PASI) 90 or 100)

- Proportion of participants achieving a PASI 75 or PGA 1 to 2 in the short term (within 6 to 8 weeks) after randomisation
  - 3 participants in Tonsillectomy group and none in no treated group achieved a PASI 75 or PGA 1 to 2 in the short term (within 6 to 8 weeks) after randomisation
  - Time of 8-week assessment1/15 (7%) patients achieved PASI 90 after 8 weeks. I cannot answer your first question better.

3. Did you have patients with secondary effects ?

- Proportion of participants with adverse effects and serious adverse effects: None in both group.
- Reply: there were no major or serious adverse effects after the tonsillectomy. One patient had a minor post-tonsillectomy bleed the day after, which resolved fast.

4. Concerning the relapse of participants:

- Proportion of participants having at least one relapse at long-term follow-up (at least one year after the start of treatment) after randomisation
  - No reply to this question
- Time of assessment: Reply: The improvement that was seen after tonsillectomy was sustained throughout the 24-month follow-up period.

4. How did you perform the sequence generation (table, computer)?

5. How did you perform the allocation concealment?

Reply:

- Twenty-nine patients met all inclusion criteria and were randomly allocated into tonsillectomy (TX) and control groups by means of a simple randomisation in a 1:1 ratio.
- A numerical code was used to identify patients and their specimens. All investigators except the study's supervisor were unaware of the treatment allocation, which was concealed until the end of the study in order to reduce study bias. The study's supervisor was responsible for the randomisation and only he had access to the numerical code.
- All included patients had strict instructions not to reveal their tonsil status to the investigator who did all the assessments.

6. What was the setting of the study ?

- No reply given

7. Did you perform throat swab before/during your study? If yes, what was the result?
Reply:

- At study entry, 8/15 of the TX Group were colonised by *Streptococci* and 6/14 of the controls. I monitored sore throat symptoms closely during the follow-up period of 24 months: The frequency of common cold and/or influenza was very similar in the 2 groups, 8/15 (53%) of the TX group and 4/14 (43%) of the controls. However, none of the tonsillectomised patients had *Streptococcal* pharyngitis during the 2-year follow-up, while 4/14 (29%) of the controls had a confirmed *Streptococcal* tonsillitis. The patients had instructions to observe and preferentially write down all episodes of sore throat and psoriasis flares. They also called me if they had pharyngitis, so that swabs could be taken. There were a few patients that reported a few episodes of sore throats

Table 2. Authors contact *(Continued)*

		and 2 patients in the TX group experienced psoriasis flare-ups. However there were no *Streptococcal* throat infections. • So during follow-up, 0/15 of the TX Group had *Streptococci* and 4/14 of the Controls, which gives us a significant difference (P = 0.0421 with Fishers exact test) **8. Concerning the proportion of participants having at least one relapse at long-term follow-up (at least one year after the start of treatment) after randomisation: did you follow the control group or only the tonsillectomy Group?** • Reply: I followed both controls and tonsillectomised patients regularly for 24 months
Dr Vincent (Vincent 1992)	No email address found	-

APPENDICES

Appendix 1. Skin Group Specialised Register (CRS) search strategy

psoria* and (tonsil* or streptococc* or antibiotic*)

Appendix 2. Cochrane Register of Studies Online (CRSO) search strategy

(psoria* and (tonsil* or streptococc* or antibiotic*)):TI,AB,KY

Appendix 3. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor: [Psoriasis] explode all trees
#2 psoria*:ti,ab,kw
#3 #1 or #2
#4 streptococc*:ti,ab,kw
#5 MeSH descriptor: [Streptococcal Infections] explode all trees
#6 MeSH descriptor: [Streptococcus] explode all trees
#7 MeSH descriptor: [Streptococcal Vaccines] explode all trees
#8 tonsillectomy:ti,ab,kw
#9 MeSH descriptor: [Tonsillectomy] explode all trees
#10 antibiotic*:ti,ab,kw
#11 MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#12 {or #4-#11}
#13 #3 and #12

Appendix 4. MEDLINE Ovid search strategy

1. psoria$.ti,ab. or exp PSORIASIS/
2. Streptococcal Infections/
3. exp Streptococcus/
4. exp Streptococcal Vaccines/
5. streptococc$.ti,ab.
6. tonsillectomy.ti,ab.
7. Tonsillectomy/
8. exp Anti-Bacterial Agents/
9. antibiotic$.ti,ab.
10. or/2-9
11. randomized controlled trial.pt.
12. controlled clinical trial.pt.
13. randomized.ab.

14. placebo.ab.
15. clinical trials as topic.sh.
16. randomly.ab.
17. trial.ti.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17
19. exp animals/ not humans.sh.
20. 18 not 19
21. 1 and 10 and 20

[Lines 11-20: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

Appendix 5. Embase Ovid search strategy

1. exp PSORIASIS/
2. psoria$.ti,ab.
3. 1 or 2
4. exp Streptococcus infection/
5. exp Streptococcus/
6. exp Streptococcus vaccine/
7. streptococc$.ti,ab.
8. tonsillectomy.ti,ab.
9. exp tonsillectomy/
10. exp antibiotic agent/
11. antibiotic$.ti,ab.
12. or/4-11
13. crossover procedure.sh.
14. double-blind procedure.sh.
15. single-blind procedure.sh.
16. (crossover$ or cross over$).tw.
17. placebo$.tw.
18. (doubl$ adj blind$).tw.
19. allocat$.tw.
20. trial.ti.
21. randomized controlled trial.sh.
22. random$.tw.
23. or/13-22
24. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
25. human/ or normal human/
26. 24 and 25
27. 24 not 26
28. 23 not 27
29. 3 and 12 and 28

Appendix 6. LILACS search strategy

psoria$ and (tonsil$ or streptococc$ or antibiotic$)

In LILACS we searched using the terms above and the Controlled clinical trials topic-specific query filter.

CONTRIBUTIONS OF AUTHORS

GD and LLC were the contact people with the editorial base.
GD and LLC co-ordinated contributions from the co-authors and wrote the final draft of the review.
GD, CD, and LLC screened papers against eligibility criteria.
GD obtained data on ongoing and unpublished studies.
GD, CD, and LLC appraised the quality (risk of bias) of papers.
GD, CD, and LLC extracted data for the review and sought additional information about papers.
GD and LLC entered data into RevMan 5.
GD and LLC analysed and interpreted data.
LLC worked on the methods sections.
LLC drafted the clinical sections of the background and responded to the clinical comments of the referees.
LLC responded to the methodology and statistics comments of the referees.

CH was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes were relevant to consumers.
LLC is the guarantor of the update.

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DECLARATIONS OF INTEREST

Gwendy Dupire: nothing to declare.
Catherine Droitcourt: nothing to declare.
Carolyn Hughes: nothing to declare.
Laurence Le Cleach: nothing to declare.

Ruth Murphy (clinical referee): "I have taken part in an advisory board with Novartis about disease prevention in Psoriasis in October 2017."

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Internal sources

- No sources of support supplied

External sources

- Association Recommandations en Dermatologie (aRED), France.
- The National Institute for Health Research (NIHR), UK.

  The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We specified in the methods section, criteria for considering studies, participants: In cases of studies including only a subset of relevant participants, we planned to include the studies only if the characteristics of patients and results were provided separately, or obtained through contact with authors.

We specified in the methods section, criteria for considering studies for this review, types of interventions, that we would consider systemic antibiotics. We considered it obvious to consider only systemic antibiotics; however, we forgot to specify it.

We decided to assess all of our outcomes, except 'Risk of having at least one relapse at long-term follow-up' at both short-term and long-term follow-up, to ensure consistency of timing across outcomes.

We deleted from the methods section, dealing with missing data: "We will also synthesise data as analysed in each trial (complete cases)." This was because we only reported numerical data in intention-to-treat analysis with imputation.

We added to the methods section, assessing risk of bias, other bias. We did not anticipated any specific other bias for this review.

We deleted: "For the older trials, the PASI 75 will probably not be available. We will calculate it based on the percentage reduction in PASI when this information is available" because it was not possible to perform it.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Ascorbic Acid [therapeutic use]; Azithromycin [therapeutic use]; Erythromycin [therapeutic use]; Penicillin V [therapeutic use]; Psoriasis [*drug therapy] [microbiology] [pathology]; Randomized Controlled Trials as Topic; Rifampin [therapeutic use]; Streptococcal Infections [*drug therapy]; Tonsillectomy; Vitamins [therapeutic use]

MeSH check words

Adolescent; Adult; Aged; Child; Humans; Middle Aged