Table 2: Characteristics of the various studies included in the systematic review.

Characteristics of the acyclovir studies included in the systematic review								
Data source/location	Study methodology Study size	Interventions	Duration of episode/ healing time (days)	Duration of pain (days)	Time to loss of crust (days)	Other findings	Author's conclusions	Risk of bias
Spruance, Crumpacker[9] 1982/USA (Analysis 1) and Spruance et al.,[16] 1982/USA (Analysis 2)	RCT Double-blind, placebo-controlled 208 patients Patients with recurrences for an average of 20 years.	**1.** 5% acyclovir ointment (polyethylene glycol base) **2.** Placebo ointment (polyethylene glycol base) Applied four times a day for 5 days. Treatment started: 0–8 hours after onset of symptoms.	**Analysis 1:** **1.** 7.8 **2.** 7.3 p=0.67 **Analysis 2:** **1.** 7.2 **2.** 7.2 p=0.67	**Analysis 1:** **1.** 2.5 **2.** 2.6 p=0.3 **Analysis 2:** **1.** 2.0 **2.** 2.0 p=0.92	**Analysis 1:** **1.** 7.2 **2.** 7.3 p=0.87 **Analysis 2:** **1.** 6.4 **2.** 7.3 p=0.87	**Analysis 1:** Duration of virus excretion (days): **1.** 1.7 **2.** 1.9 p=0.24 **Analysis 2:** Median titre of virus in lesion decreased by 1.5 log pfu/d in the acyclovir group versus 0.2 log pfu/d in the placebo group.	**Analysis 1:** No clinical benefit from treatment with acyclovir ointment was observed. **Analysis 2:** Treatment with acyclovir decreased the median titre of viral lesions, but no clinical benefits were observed.	**Analysis 1:** High risk: Attrition bias No mention of withdrawals or exclusion criteria **Analysis 2:** Low risk
Whitley et al.,[17] 1982/USA	RCT Double-blind, placebo-controlled 48 patients (all immunocompromised) Number of previous recurrences not mentioned.	**1.** 5% acyclovir ointment (polyethylene glycol base) **2.** Placebo ointment (polyethylene glycol base) Applied four times a day for 10 days. Treatment started: lesions present at time of enrolment.	**1.** 15.12±0.49 **2.** 15.57±0.51 After 1 month, 20% had lesions that failed to heal.	**1.** 15.11±0.40 **2.** 15.8±0.80	NA	Duration of viral shedding (day from entry to two consecutive negative cultures): **1.** 2.50±0.49 **2.** 9.40±3.09 p=0.001	In immunocompromised patients, acyclovir therapy resulted in no difference in time to total healing when compared to placebo but did result in accelerated elimination of virus from the lesions.	Low risk
Fiddian et al.,[18] 1983/UK	RCT Double-blind, placebo-controlled 13 patients 31 cases Patients with at least two recurrences in the past year.	**1.** 5% acyclovir ointment (polyethylene glycol base) **2.** Placebo ointment (polyethylene glycol base) Applied five times a day for 5 days. Treatment started at onset of prodromal symptoms.	**1.** 6.0 **2.** 8.0 p<0.05	NA	**1.** 3.0 **2.** 4.0 p<0.05	NA	Acyclovir had a therapeutic effect in patients with recurrent herpes labialis.	Low risk
Fiddian et al.,[19] 1983/UK	RCT Double-blind, placebo-controlled 49 patients 74 cases Patients with at least two recurrences in the past year.	**1.** 5% acyclovir cream **2.** Placebo cream Applied five times a day for 5 days. Treatment started at onset of symptoms.	**1.** 4.0 **2.** 6.0 p=0.02	NA	**1.** 1.0 **2.** 2.0 p=0.02	Percentage of abortive lesions: **1.** 8.0% **2.** 2.0% p=0.03 Duration of all symptoms (days): **1.** 1.0 **2.** 3.0 p=0.07 Duration of itching (days): **1.** 0.5 **2.** 1.0 p=0.21 Percentage of lesions with itching: **1.** 8.0% **2.** 15.0% p=0.06	Acyclovir cream was well tolerated and effective for the treatment of herpes labialis.	Low risk
van Vloten et al.,[20] 1983/Netherlands	RCT Double-blind, placebo-controlled 36 patients 60 cases Patients with an average of 6–7 recurrences per year.	**1.** 5% acyclovir cream (propylene glycol base) **2.** Placebo cream (propylene glycol base) Applied five times a day for 5 days. Treatment started at onset of symptoms.	All lesions: **1.** 5.4 **2.** 6.6 p=0.051 First lesion: **1.** 5.8 **2.** 8.3 p=0.022	**1.** 1.7 **2.** 1.7 p=0.76	**1.** 2.1 **2.** 2.0 p=0.53	Time to vesication (days): **1.** 1.1 **2.** 1.2 p=0.22 Duration of vesication (days): **1.** 1.6 **2.** 2.3 p=0.016 Duration of itching (days): **1.** 0.8 **2.** 1.0 p=0.48	Topical application of 5% acyclovir cream reduced total healing time for recurrent herpes labialis infections.	High risk: Attrition bias No mention of withdrawals or exclusion criteria.
Spruance et al.,[21] 1984/USA	RCT Double-blind, placebo-controlled 69 patients Patients with at least three recurrences in the past year.	**1.** 10% acyclovir ointment (polyethylene glycol base) **2.** Placebo ointment (polyethylene glycol base) Applied eight times a day for 5 days. Treatment started in the prodrome or erythema stage.	**1.** 6.0 **2.** 5.2 p=0.61	**1.** 2.0 **2.** 2.3 p=0.52	NA	Time to last positive viral culture (days): **1.** 1.1 **2.** 1.9 p=0.47 Progression to vesicle ulcer **1.** 91.0% **2.** 75.0% p=0.15	Topical 10% acyclovir was not of clinical benefit to persons with recurrent herpes labialis, despite initiation of therapy in the prodrome or erythema stage.	Low risk
Shaw et al.,[22] 1985/UK	RCT Double-blind, crossover, placebo-controlled 72 patients 72 cases Patients with at least three recurrences in the past year.	**1.** 5% acyclovir cream (propylene glycol base) **2.** Placebo cream (propylene glycol base) Applied five times a day for 5 days. Treatment started at onset of prodromal symptoms.	**1.** 9.0 **2.** 10.0 p=0.82	NA	**1.** 5.0 **2.** 5.0 p=0.56	Duration of all symptoms (days): **1.** 5.0 **2.** 6.0 p=0.33 Median time to first crust (days): **1.** 2.0 **2.** 2.0 p=0.64	No significant clinical benefit from treatment with acyclovir cream when compared to placebo. Untreated episodes lasted longer than both groups, indicating possible beneficial effect of the propylene glycol base.	Low risk
Raborn et al.,[23] 1989/Canada	RCT Double-blind, placebo-controlled 61 patients 102 cases Number of previous recurrences not mentioned.	**1.** 5% acyclovir cream in modified aqueous cream vehicle **2.** Modified aqueous cream vehicle placebo Applied every 4 hours for 5 days. Treatment started within 1 hour of onset of prodromal symptoms.	**First lesion:** **1.** 7.0±2.8 **2.** 7.7±4.0 **Second lesion:** **1.** 7.1±3.0 **2.** 8.1±3.3	**First lesion:** **1.** 1.1±0.2 **2.** 1.0±0.2 **Second lesion:** **1.** 1.2±0.6 **2.** 1.1±0.3	**First lesion:** **1.** 6.1±2.6 **2.** 7.1±0.4 **Second lesion:** **1.** 7.5±2.8 **2.** 7.3±2.8	Cross-sectional area (mm^2): **First lesion:** Day 1: **1.** 10.2±13.0 **2.** 22.8±32.6 Day 5: **1.** 8.3±12.5 **2.** 21.6±37.0 **Second lesion:** Day 1: **1.** 14.5±13.2 **2.** 18.6±14.7 Day 5: **1.** 6.1±7.3 **2.** 12.9±14.2	Acyclovir in a modified aqueous cream vehicle showed a trend towards accelerated healing but there was not a significant difference to placebo.	Low risk
Raborn et al.,[24] 1989/Canada	RCT Double-blind, placebo-controlled 80 patients 120 cases Number of previous recurrences not mentioned.	**1.** 5% acyclovir ointment (polyethylene glycol base) **2.** Placebo ointment (polyethylene glycol base) Applied every 2 hours for 5 days. Treatment started within 12 hours for the first lesion and within 1 hour for the second lesion.	**First lesion:** **1.** 7.9±4.0 **2.** 8.8±3.7 **Second lesion:** **1.** 7.7±2.7 **2.** 7.8±3.7	**First lesion:** **1.** 1.08±0.2 **2.** 1.04±0.2 **Second lesion:** **1.** 1.07±0.3 **2.** 1.05±0.3	**First lesion:** **1.** 8.9±3.6 **2.** 7.9±2.7 **Second lesion:** **1.** 7.6±2.5 **2.** 8.1±3.2	Cross-sectional area from Day 1 to Day 5 decreased by 34% in the placebo group and increased by 24% in the acyclovir group.	Acyclovir ointment failed to show better clinical healing effects than placebo in both the first and second documented episodes.	Low risk
Horwitz et al.,[25] 1999/Jerusalem	RCT Double-blind active comparator and placebo-controlled 40 patients Patients with an average of four to five recurrences per year.	**1.** 5% acyclovir in novel liposomal carrier **2.** 5% acyclovir cream **3.** Placebo cream Applied four times a day until healed. Treatment started at onset of symptoms.	NA	NA	**1.** 1.6 **2.** 4.3 **3.** 4.8 p<0.05	Loss of crust (days): **1.** 3.5 **2.** 6.4 **3.** 6.4	The novel liposomal drug carrier improved the clinical efficacy of acyclovir.	Low risk
Spruance et al.,[26] 2002/USA (Study 1)	RCT Double-blind, placebo-controlled 1,051 patients 686 cases Patients with at least three recurrences in the past year.	**1.** 5% acyclovir cream (with propylene glycol) **2.** Placebo cream (with propylene glycol) Applied five times a day for 4 days. Treatment started within 1 hour of onset of prodromal symptoms.	**1.** 4.3 **2.** 4.8 p=0.01	**1.** 2.9 **2.** 3.2 p=0.024	NA	Drug efficacy could be seen in patients who started treatment in either the early or late lesion stage.	Acyclovir cream had highly statistically significant effects on the duration of episode and lesion pain when compared to placebo.	Low risk
Spruance et al.,[26] 2002/USA (Study 2)	RCT Double-blind, placebo-controlled 1,028 patients 699 cases Patients with at least three recurrences in the past year.	**1.** 5% acyclovir cream (with propylene glycol) **2.** Placebo cream (with propylene glycol) Applied five times per day for 4 days. Treatment started within 1 hour of prodromal symptoms.	**1.** 4.6 **2.** 5.2 p=0.007	**1.** 3.1 **2.** 3.5 p=0.027	NA	NA	Acyclovir cream had highly statistically significant effects on the duration of episode and lesion pain when compared to placebo.	Low risk
Bodsworth et al.,[27] 2003/Slovakia	RCT Double-blind, active-comparator 367 patients Patients with an average of four recurrences in the past year.	**1.** 5% acyclovir cream **2.** 5% acyclovir/2% lidocaine cream Treatment start time was not mentioned.	**1.** 4.44 **2.** 4.82	NA	NA	Time to pain relief (mins): **1.** 53.5 **2.** 31.9 Significant relief after 4 hours (%): **1.** 56.0 **2.** 50.0	A trend towards a shorter time to meaningful pain relief was observed with acyclovir and lidocaine when compared to acyclovir alone but was not statistically significant.	Low risk
Zschocke et al.,[28] 2008/Germany	RCT Open-label, comparator-controlled 74 patients 74 cases Patients with at least three recurrences in the past year	**1.** Silica gel **2.** 5% acyclovir cream (Zovirax) Applied five times a day. Treatment started within 24 hours.	NA	NA	NA	Efficacy rated by physician (rated 1–5): Day 4: **1.** 4.1±0.7 **2.** 4.2±0.7 Day 10: **1.** 4.3±1.0 **2.** 4.4±0.7 Efficacy rated by patient (rated 1–5): Day 2: **1.** 4.2±0.9 **2.** 4.2±0.8 Day 4: **1.** 4.4±0.8 **2.** 4.4±0.8 Day 7: **1.** 4.4±0.7 **2.** 4.3±0.7 Day 10: **1.** 4.2±1.0 **2.** 4.4±0.6	Silica gel was comparable to acyclovir cream in the effective treatment of herpes labialis. In comparison with acyclovir cream, the patients reported that the beneficial effect of silica gel could be noticed more quickly.	High risk Blinding of outcome assessments and blinding of participants and personnel: No blinding procedures were undertaken.

Characteristics of the penciclovir studies included in the systematic review								
Data source/location	Study methodology Study size	Interventions	Duration of episode/ healing time (days)	Duration of pain (days)	Time to loss of crust (days)	Other findings	Author's conclusions	Risk of bias
Spruance et al.,[29] 1997/USA One of the 2 trials conducted by Raborn et al.,[32] 2002/Canada	RCT Double-blind, placebo-controlled 1,573 patients 1,573 cases Patients with at least three recurrences in the past year.	**1.** 1% penciclovir cream **2.** Placebo cream Applied every 2 hours while awake for 4 days. Treatment started within 1 hour of first sign or symptom.	**1.** 4.8 **2.** 5.5	**1.** 3.5 **2.** 4.1	NA	Duration of viral shedding (days) **1.** 3.0 **2.** 3.0	Healing and pain resolution occurred faster in penciclovir-treated patients at all stages of lesions.	Low risk
Femiano et al.,[30] 2001/UK	QRT Unblinded, no placebo, method of randomisation unclear 40 patients 40 cases Patients with at least five recurrences in the past year.	**1.** 5% acyclovir cream **2.** 1% penciclovir cream Applied every 2 hours while awake for 4 days. Prodromal therapy treatment started during prodromal phase. Disease therapy treatment started after the appearance of vesicles.	NA	Prodromal therapy: **1.** 5.0 **2.** 4.0 Disease therapy: 20% reduction of the duration of pain in the penciclovir arm compared to the acyclovir arm.	NA	NA	Penciclovir was superior to acyclovir.	Low risk
Lin et al.,[31] 2002/China	RCT Double-blind, placebo-controlled 225 patients 225 cases Patients with first episode and a history of recurrence.	**1.** 1% penciclovir cream **2.** 3% acyclovir cream Applied five times a day up to 7 days. Treatment started within 24 hours of lesion onset.	NA	NA	NA	Time to resolution of all symptoms (days): **1.** 3.0 **2.** 3.0	Topical 1% penciclovir cream was as convenient and as effective as 3% acyclovir cream.	Low risk
Raborn et al.,[32] 2002/Canada	RCT Double-blind, placebo-controlled 3,057 patients A combination of two trials. Patients with at least three recurrences in the past year.	**1.** 1% penciclovir cream **2.** Placebo cream Applied every 2 hours while awake for 4 days. Treatment started within 1 hour of noticing the first sign/symptom.	Penciclovir arm lost lesions 31% faster than the placebo arm (p=0.0001).	Penciclovir arm had 28% faster resolution of lesion pain compared to the placebo arm (p=0.0001).	NA	NA	Penciclovir cream significantly outperformed the placebo in healing lesions and resolution of pain.	Low risk

Characteristics of the docosanol studies included in the systematic review								
Data source/location	Study methodology Study size	Interventions	Duration of episode/ healing time (days)	Duration of pain (days)	Time to loss of crust (days)	Other findings	Author's conclusions	Risk of bias
Habbema et al.,[33] 1996/Netherlands	RCT Double-blind, placebo-controlled 63 patients 98 cases Patients with at least three recurrences in the past year.	**1.** 10% n-docosanol cream **2.** Placebo cream Applied five times a day up to 10 days. Treatment started at the first sign/symptoms of a recurrence.	**1.** 5.7 **2.** 7.3 p=0.02	NA	NA	NA	Docosanol cream significantly shortened healing time when compared to placebo.	Unclear risk Details of randomisation and blinding were not included.
Sacks et al.,[34] 2001/Canada	RCT Double-blind, placebo-controlled 737 patients Patients with at least two recurrences in the past year.	**1.** 10% docosanol cream **2.** Placebo cream Applied five times a day for up to 10 days. Treatment started within 12 hours of first signs/symptoms.	**1.** 97.8 hours **2.** 115.3 hours p=0.23	NA	**1.** 86.7 hours **2.** 94.5 hours p<0.001	Time to cessation of all symptoms in the docosanol arm was 14.3 hours faster than placebo.	Docosanol cream was safe and effective.	Low risk

NA: data not available; QRT: quasi-randomised trial; RCT: randomised controlled trial.