Acyclovir for treating varicella in otherwise healthy children and adolescents (Review)

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[Intervention Review]

Acyclovir for treating varicella in otherwise healthy children and adolescents

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ABSTRACT

Background

Acyclovir has the potential to shorten the course of illness which may result in reduced costs and morbidity associated with chickenpox.

Objectives

To examine the evidence evaluating the efficacy of acyclovir in alleviating symptoms of chickenpox and shortening the duration of illness.

To examine complications of chickenpox and adverse effects associated with acyclovir as reported in the relevant trials.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* 2008, issue 3) which contains the Acute Respiratory Infections Group's Specialized Register, MEDLINE (1950 to Septemer Week 3, 2008), and EMBASE (1974 to September 2008). The reference lists of all relevant articles were reviewed.

Selection criteria

Randomized controlled trials that evaluated otherwise healthy children zero to 18 years of age, with chickenpox.

Data collection and analysis

Two review authors independently reviewed the studies for eligibility. Two review authors independently assessed methodological quality of the relevant studies using the Jadad scale and allocation concealment. Differences were resolved by consensus. Data were extracted by one review author using a structured form and checked by a second.

Continuous data were converted to the weighted mean difference (WMD). Weighted mean differences were combined into an overall estimate using random effects. There were too few studies to consider exploring statistical heterogeneity between studies (i.e., differences in reported effects), formally, or to assess for publication bias.

Main results

Three studies were included. Study quality was three (n = 2) and four (n = 1) on the Jadad scale. Acyclovir was associated with a reduction in the number of days with fever (-1.1 days, 95% CI -1.3 to -0.9) and in reducing the maximum number of lesions (-76 lesions, -145 to -8). Results were less supportive with respect to the number of days to no new lesions and the number of days to the relief of itching. There were no clinically important differences between acyclovir and placebo with respect to complications associated with chickenpox or adverse effects associated with the treatment.

Authors' conclusions

Acyclovir appears to be effective in reducing the number of days with fever and the maximum number of lesions among otherwise healthy children with chickenpox. The results were less convincing with respect to the number of days to no new lesions and relief of itchiness. The clinical importance of acyclovir treatment in otherwise healthy children remains uncertain.

PLAIN LANGUAGE SUMMARY

Acyclovir can reduce the number of days with fever in otherwise healthy children with chickenpox, but its effect on sores and itching is not yet certain

Chickenpox (varicella) is caused by a virus. It begins with a fever, followed by a rash of red pimples which become itchy sores that form scabs. Chickenpox usually affects children from one to 14 years. In young babies, adults or people with impaired immune system, chickenpox is more severe. Treatments include lotions to relieve itchiness, paracetamol (acetaminophen) for fever and the antiviral drug acyclovir. The review of trials found that acyclovir reduces the number of days of fever from chickenpox in otherwise healthy children, usually without adverse effects. It is not clear whether it improves sores and itching.

BACKGROUND

Description of the condition

Varicella, or chickenpox, is a common, highly contagious illness caused by the varicella-zoster virus (VZV) (Brunell 1987). It is primarily a disease of early childhood with 90% of cases occurring in children 1 to 14 years of age (Preblud 1984). The disease spreads by direct person-to-person contact of open lesions or airborne droplets (Brunell 1987) and tends to increase in severity with each subsequent case within a household (Ross 1962). The period of transmission begins one to two days before any rash appears (Avery 1994) and continues for the first five to six days (Brunell 1987). The disease is more severe in neonates (Gershon 1975; Meyers 1974), adults (Preblud 1981), and individuals who have impaired immune systems (Feldhoff 1981; Feldman 1975). After one episode of varicella, individuals usually have lifelong immunity (Brunell 1987).

Chickenpox is generally self-limiting in young children and is manifested by fever, mild constitutional symptoms, and an itchy, vesicular rash. Symptoms usually appear 11 to 20 days after exposure to VZV (Preblud 1984). The rash most often appears in three successive crops of lesions numbering on average 300 to 400 (CDC 2001). The lesions progress from macules through to crusted lesions over a three-day period (Feder 1990). The rash is most commonly distributed over the trunk, scalp and face. Diagnosis can be made clinically by the rash characteristic of chickenpox (Preblud 1984) and a history of contact (Brunell 1987).

Complications of chicken pox are varied and may occur in five to ten per cent of all patients. Complications among otherwise healthy children are rare (Conway 1993; Mouzard 1998) but are more common among neonates, adults and immunocompromised individuals (Preblud 1984; Rotbart 1993). Data with respect to complication rates among specific subgroups are lacking. Complications primarily involve the skin, the central nervous system and the respiratory system (Drwal-Klein 1993; Mouzard 1998). The most frequent complication is bacterial infection secondary to cutaneous lesions (Mouzard 1998; Preblud 1984). The most common neurological complications are cerebellar ataxia and encephalitis. Complications of the respiratory system include pneumonia and upper respiratory tract infections (particularly otitis media).

Description of the intervention

Traditional treatment for chickenpox is symptomatic, through the use of lotions to relieve itchiness (Brunell 1987) and acetaminophen to reduce fever and pain (Avery 1994). Newer treatments include immunoglobulins, vaccines, and anti-viral drugs for the prevention of chicken pox, as well as immunoglobulins and anti-viral drugs to moderate and shorten the course of the disease. As an anti-viral drug, acyclovir prevents the replication of the VZV (Arvin 1987; Laskin 1984) and has the potential to eradicate VZV and relieve symptoms more rapidly. Since the drug is only absorbed by the cells that are infected with the virus, acyclovir has minimal adverse effects (Croze 1994). Some reported adverse effects to the oral administration of acyclovir include nausea, vomiting, diarrhea and vertigo (Croze 1994).

Why it is important to do this review

The economic burden associated with chickenpox results from costs associated with hospitalizations, physician visits, prescription and nonprescription medications, and lost income by caregivers who must remain at home during the course of the child's illness (Brunell 1991). It has been estimated that lost wages account for more than 95% of the total costs (Preblud 1986). The US Centers for Disease Control and Prevention recommend that children remain at home for six days after the rash onset (CDC 2001). These recommendations vary according to local public health authorities; others advocate return to normal activity earlier, particularly with milder forms of the disease (Moore 1991). The Canadian Pediatric Society recommends that children return to school as soon as they feel well enough to resume normal activities, regardless of the state of the rash (CPS 1999). Because of the potential costs associated with lost time from work by primary caregivers, an intervention that reduces the length of illness may be well received.

OBJECTIVES

The primary objective was to assess the evidence on the efficacy of acyclovir in

1. alleviating symptoms (number of lesions, itchiness, fever);
2. shortening the duration of the illness among otherwise healthy children less than 19 years of age.

The secondary objective was to examine complications of chickenpox and adverse effects associated with acyclovir, as reported in the relevant efficacy trials.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomized controlled trials (RCTs) were included. This was defined as studies which were described by the authors as randomized anywhere in the manuscript. All identified trials, published or unpublished, were eligible. No language restrictions were applied.

Types of participants

Studies that evaluated otherwise healthy children zero to 18 years of age with chickenpox were included. Since chickenpox is primarily a childhood disease (Preblud 1984), we chose not to include studies that specifically evaluated adults.

Types of interventions

Acyclovir compared with a placebo group.

Types of outcome measures

Primary outcomes

The amount of time to no new lesions from the point of randomization.

Secondary outcomes

The maximum number of lesions;
Time to resolution of fever (37.8°C);
Time to resolution of itching.
All reported complications from chickenpox and adverse events related to the use of acyclovir were recorded.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* 2008, issue 3) which contains the Acute Respiratory Infections Group's Specialized Register, MEDLINE (1950 to Septemer Week 3 2008), and EMBASE (1974 to September 2008).
The reference lists of all relevant articles were reviewed. The primary author of relevant studies and the pharmaceutical company that manufactures acyclovir were contacted. The MEDLINE search strategy was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised controlled trials (Lefebvre 2008).

MEDLINE (OVID)

1 Chickenpox/
2 chickenpox.tw.
3 chicken pox.tw.
4 varicella.tw.
5 or/1-4
6 exp Acyclovir/
7 acyclovir*.tw.
8 aciclovir*.tw.
9 or/6-8
10 (infant or child or adolescent or minors or puberty or pediatrics or schools).sh.
11 (infant* or infancy or newborn* or baby* or babies* or neonat* or preterm* or prematur* or postmatur* or child* or schoolchild* or school age* or preschool* or kid or kids or toddler* or adoles* or teen* or boy* or girl* or minors* or pubert* or pubescen* or prepubescen* or pediatric* or paediatric* or nursery school* or kindergar* or primary schoool* or secondary school* or elementary school* or high school* or highschool*).tw.
12 10 or 11
13 9 and 12 and 5

Searching other resources

The reference lists of all identified articles were reviewed for potentially relevant studies. A letter was sent to the primary author of relevant studies as well as the pharmaceutical company that manufactures acyclovir (GlaxoWellcome) in order to identify any other relevant trials, published or unpublished.

Data collection and analysis

Selection of studies

Two review authors selected potentially relevant studies from the lists of titles and abstracts generated from the database searches. All potentially relevant studies were retrieved as complete manuscripts and then independently reviewed by two review authors. Differences regarding which studies to include were resolved by consensus reached after discussion.

Data extraction and management

Data were extracted using a structured form that captured the following information: patient demographics; patient status (inpatient or outpatient); the intervention (including dosage and route of administration); outcomes (i.e. length of time from randomization to no new lesions, crusting, no fever and cessation of itching); funding source; and, whether the studies used an intention-to-treat analysis. All complications from chickenpox reported in the studies were recorded. As well, information on all adverse effects related to the use of acyclovir was collected. Two review authors extracted data independently and results were compared. Differences were resolved by referring to the original paper.

Assessment of risk of bias in included studies

All relevant studies were masked by obscuring the authors' names and institutions, the locations of the study, reference lists, journal of publication and any other potential identifiers. Each of the included studies were evaluated using the previously validated Jadad five point scale to assess randomization (zero to two points), double blinding (zero to two points) and withdrawals and dropouts (zero to one point) (Jadad 1996). Concealment of allocation was described as adequate, inadequate or unclear (Schulz 1995). Two review authors independently assessed quality. Differences were resolved by consensus.

Measures of treatment effect

Continuous data (such as duration of symptoms in days and maximum number of lesions) were converted to the weighted mean difference (WMD). Medians were substituted for means for all outcomes in the study by Balfour et al (Balfour 1990). Means were calculated from proportions of patients remaining with lesions (Balfour 1992; Dunkle 1991), fever (Balfour 1992; Dunkle 1991), and itching (Dunkle 1991). Day five (fever, pruritis) and day seven (new lesions) were used as the last possible day for the event to occur. These substitutions give less conservative estimates of variance. Inter-quartile ranges, that is, 25th to 75th percentile were converted into standard deviations and pooled for both treatment groups (Balfour 1990). Imputing using upper bound p-values gave conservative variances in both treatment groups (Balfour 1992; Dunkle 1991) for the maximum number lesions.

Risk ratios were used to combine dichotomous outcomes (such as skin complications). Results were combined into an overall estimate using random effects. Fixed-effect results were presented if statistical significance changed.

Since the adverse event data were not independent (the numbers were reported by event not by patient), risk differences could not be calculated nor any further analysis.

Assessment of heterogeneity

We quantified statistical heterogeneity using the I^2 statistic (Higgins 2003). Power analyses for complications were exploratory. Individual study results were pooled and chi-square tests were the bases of the power analyses. There were too few studies to consider exploring statistical heterogeneity, that is, differences in reported effects between studies formally by performing subgroup analyses.

Assessment of reporting biases

There were too few studies to consider exploring publication bias.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Seven hundred and thirty-nine unique references were retrieved. There were no additional studies identified through contacting authors or the pharmaceutical company.

Included studies

Thirteen studies were identified as being potentially relevant. Nine of the studies were excluded because they were not RCTs; one RCT was excluded because it evaluated immediate versus delayed antiviral treatment therefore all patients received acyclovir (Balfour 2001). Three studies were included in this review (*see* 'Characteristics of included studies' table). There was 100% agreement between the review authors with respect to study relevance.

The three relevant trials were conducted in the United States and were published in English. All three studies were placebo-controlled and evaluated the efficacy of acyclovir among immunocompetent children in an outpatient setting. The mean age of the children in the three trials ranged from 5.2 to 14.8 years; the minimum age was two years and the maximum was 18 years. The studies varied in size with 105, 815, and 68 patients, respectively (Balfour 1990; Balfour 1992; Dunkle 1991).

Risk of bias in included studies

The quality scores of included studies, as measured by the Jadad scale, were four in one trial (Balfour 1990) and three in the remaining two trials (Balfour 1992; Dunkle 1991). All three studies were described as being randomized and double-blind. Only one trial described a detailed and appropriate method of randomization (Balfour 1990). One trial (Balfour 1990) described an appropriate method of double-blinding. Two of the three trials adequately discussed withdrawals (Balfour 1992; Dunkle 1991). Allocation concealment was unclear in all three trials. Two studies (Balfour 1992; Dunkle 1991) performed intention-to-treat analyses on adverse events and on a select few of the remaining outcomes. All three studies received pharmaceutical sponsorship. In addition, two studies received financial support from other external sources (Balfour 1990; Balfour 1992).

Effects of interventions

Primary outcome (number of days to no new lesions)

Two of three studies found a statistically significant advantage to taking acyclovir. However, overall the number of days to no new lesions was not significant (-0.8 days, 95% CI -1.6 to 0.02). The fixed-effect estimate was significant (-1.0 days, -1.2 to -0.8). Also, removing the study (Balfour 1990) where we substituted the median for the mean gave an overall significant result (-1.2 days, -1.4 to -1.0) and heterogeneity was reduced from 91% to 0%.

Additional outcomes

The results with respect to the maximum number of lesions were consistent in direction, however, only two of three studies reported a significant difference favoring treatment with acyclovir. The overall result was significant (-76 lesions, -145 to -8). Removing Balfour 1990 again reduced the heterogeneity from 84% to 0%. This sensitivity result was (-44 lesions, -72 to -16).

The number of days to no fever was reduced by treatment with acyclovir in all three trials: -1.1 days (-1.3 to -0.9). Heterogeneity was absent and the sensitivity result with Balfour 1990 removed was largely unmodified.

The number of days to relief of itching was reported in two studies. Dunkle 1991 found a 0.8 day advantage with acyclovir treatment (95% CI -1.0 to -0.7). Balfour 1990 found no advantage (0 days; 95% CI -0.6 to 0.6). The overall result was insignificant (-0.5 days, -1.3 to 0.3) and heterogeneous (I^2 = 86%). The fixed-effect result was significant (-0.8 days, -0.9 to -0.6).

Sensitivity analysis

The Balfour 1990 study results were imputed from non-parametric data and may have produced less precise results. If so, as shown above both outcomes that were insignificant became significant when Balfour 1990 was removed. Also, in the two outcomes that had results from all three studies, when Balfour 1990 was removed, heterogeneity was also removed. This may indicate a stronger advantage for taking acyclovir.

Adverse effects

Reported adverse effects involving the gastrointestinal system included: anorexia (23 acyclovir; 30 placebo); diarrhea (25 acyclovir; 18 placebo); nausea/vomiting (11 acyclovir; 10 placebo); stomachache/abdominal pain (22 acyclovir; 14 placebo); flatulence (two acyclovir; four placebo).

Those involving the respiratory system included: runny nose (18 acyclovir; 23 placebo); cough (23 acyclovir; 29 placebo); ear pain/redness (five acyclovir; six placebo); sore throat (24 acyclovir; 33 placebo).

The following adverse effects involving the skin were noted: hives (one acyclovir; one placebo); rash other than varicella (three acyclovir; one placebo).

Other reported effects were: conjunctivitis (acyclovir eight; placebo 11); headache (acyclovir 21; placebo 22); malaise (acyclovir 25; placebo 28); irritability (acyclovir one); skin odor (acyclovir one); insomnia (acyclovir five; placebo five); nose bleed (acyclovir two; placebo one); dizziness (acyclovir three; placebo two); restlessness (acyclovir one; placebo one); arthralgia (placebo three); frequency (placebo one); night sweats (placebo one); hyperkinesia (acyclovir one; placebo one); pain (acyclovir one); spasmodic hand movements (acyclovir one; placebo one).

Complications

Complications were grouped by those involving the skin, central nervous system, or respiratory system. Fifteen patients developed secondary bacterial skin infections (five acyclovir; 10 placebo).

Central nervous system complications included cerebellar ataxia (one placebo) and meningoencephalitis (one placebo).

Respiratory ailments included pneumonia (one acyclovir), otitis media (two acyclovir; four placebo), pharyngitis (two acyclovir; two placebo), and bronchitis (one acyclovir).

There were no significant differences between the treatment groups with respect to all the grouped complications arising from chickenpox. Skin complications gave the largest simply pooled difference at one per cent. The review is not sufficiently powered to detect this difference; however, the size of difference is not clinically important. The central nervous system and respiratory system simply pooled differences were less than 0.5%.

DISCUSSION

Efficacy of acyclovir

This systematic review of acyclovir for the treatment of chickenpox in otherwise healthy children supports a reduction in disease severity and a shorter course of disease. This is demonstrated by a one-day reduction in the number of days with fever and significantly fewer lesions. The results for Balfour 1990 were imputed from non-parametric data and may therefore be less precise. The evidence is strengthened when this study is removed: a significant one-day reduction in time to no new lesions and in relief of itching. In this situation the median may be an inappropriate substitution for the mean because time to event outcomes are often skewed. The quality of the included studies was relatively good as measured by the Jadad scale thus having a low risk of bias.

Complications and adverse effects

There were no clinically important differences between acyclovir and placebo with respect to complications associated with chickenpox or adverse effects associated with the treatment.

Meta-analysis

We identified only three studies relevant to this review. Because of the small number of studies and their different study populations, we did not feel that it was appropriate to explore heterogeneity formally. Publication bias was also not assessed because of the small number of trials.

Implications for practice

Though these studies have demonstrated the efficacy of acyclovir, the clinical importance of acyclovir treatment in otherwise healthy children remains controversial. The debate in the literature features four common themes.

First, the treatment appears to confer, at best modest benefits for a disease that is self-limiting and has few complications in otherwise healthy children (Brunell 1991; Mouzard 1998).

Second, the efficacy of acyclovir has been demonstrated when treatment was initiated within 24 hours of rash onset. Various authors have criticized this as being impractical in that many patients may not detect disease onset and not obtain a prescription until well after this 24-hour window (Brunell 1991; Drwal-Klein 1993; McKendrick 1995). In a recent trial, Balfour et al showed that patients who initiated acyclovir within 24 hours of rash onset showed better clinical response to therapy compared to those who initiated treatment at 48 or 72 hours (Balfour 2001). Further, patients who began therapy after 48 hours responded more favorably than those who started after 72 hours. Others have questioned the extent of compliance with the study protocols (i.e., four doses per day) (Balfour 1995; McKendrick 1995). Alterations in compliance may dilute already moderate results (Brunell 1991).

Third, while no formal cost-benefit analysis has been conducted, various critics have suggested that treatment benefits do not justify the additional costs of the drug as well as the physician visits required to obtain a prescription (Balfour 1995; McKendrick 1995; Mouzard 1998). If treatment with acyclovir does not significantly alter the complication rate of varicella, then the rate of hospitalizations and their associated costs are unlikely to change (Ghirga 1992). In addition, only one study specifically measured the impact of acyclovir treatment on school attendance (Balfour 1990). This study found no difference in the number of days missed from school between the acyclovir and placebo groups. Treatment with acyclovir may not have a substantial impact on the number of days missed from school as public health authorities in some jurisdictions move towards more permissive policies regarding school attendance following VZV infection (CPS 1999).

Finally, concerns have been raised regarding the emergence of an acyclovir resistant strain of VZV (Balfour 1995; Ghirga 1992; McKendrick 1995; Mouzard 1998). There is evidence to suggest that resistant strains of VZV do not occur (Balfour 2001; Cole 1986; Englund 1990).

At present, there appear to be too many unanswered questions to advocate the widespread use of acyclovir in otherwise healthy children. The treatment of chickenpox with acyclovir may become immaterial as public health authorities worldwide move towards adopting the varicella vaccine to protect against VZV (CDC 2001; Drwal-Klein 1993).

AUTHORS' CONCLUSIONS

Implications for practice

- When initiated within 24 hours after rash onset, treatment with acyclovir shows a therapeutic benefit in reducing the length of time with fever and the number of maximum lesions in immunocompetent children; results are less convincing with respect to the number of days to no new lesions, the maximum number of lesions and relief of itchiness.

- There were no clinically important differences in the number of complications and adverse effects among the acyclovir and placebo groups.

- The magnitude of the results does not support the widespread use of acyclovir among young immunocompetent children in which chickenpox is self-limiting and results in few complications.

Implications for research

- A comprehensive cost-benefit analysis is required.

- There were few data available on the impact of acyclovir on the number of days missed from school or work. If one of the more important advantages of acyclovir is to allow individuals to return to their activities sooner, this needs to be specifically evaluated and documented.

- There is no evidence regarding different doses of acyclovir treatment. Smaller doses may reduce costs and increase compliance.

- Further research should focus on the identification and treatment of immunocompetent children who are at higher risk of more severe disease (for example, those with chronic respiratory conditions, children exposed through intrafamilial contact).

- Other antivirals against varicella with improved bioavailability are now available (i.e., valaciclovir and famciclovir) and should be studied in pediatric populations.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Balfour 1990

Methods	Randomized, double blind Sample size at entry Acyclovir - 50 Placebo - 52
Participants	Country: USA Immunocompetent children with laboratory confirmed varicella Number enrolled: 105 Mean age: 8.05 years Sex: 48 males; 54 females Withdrawals: three (treatment group not specified)
Interventions	Acyclovir: age five to seven (20 mg/kg), age seven to twelve (15 mg/kg), age 12 to 16 (10 mg/kg); four times/day for a minimum of five days and maximum of seven Placebo Patients enrolled within 24 hours of rash onset
Outcomes	Days to fever, crusting, no new lesions, maximum number of lesions, decrease in number of lesions and cessation of itching Maximum number of lesions
Notes	Quality score = four IMPUTATIONS Time to no new lesions: medians substituted for means, standard deviation (SD) imputed from interquartile range (IQ) Maximum Number of Lesions: medians, substituted for means, SD imputed from p-value Time to No Fever: medians substituted for means, SD imputed from p-value Time to No Itching: medians substituted for means, SD imputed from IQ

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Balfour 1992

Methods	Randomized, double blind Sample size at entry Acyclovir - 32 Placebo - 36

Balfour 1992 (*Continued*)

Participants	Country: USA Immunocompetent children with laboratory confirmed varicella Number enrolled: 68 Mean age: 14.8 years Sex: 27 males; 35 females Withdrawals: one acyclovir; five placebo
Interventions	Acyclovir: 800 mg four time/day for five days Placebo Patients enrolled within 24 hours of rash onset
Outcomes	Days to maximum number of lesions and cessation of itching Maximum number of lesions Residual lesions at day 28
Notes	Quality score = three IMPUTATIONS Time to No New Lesions: summary measures imputed from scanned graph Maximum Number of Lesions: SD imputed from p-value Time to No Fever: summary measures imputed from scanned graph

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Dunkle 1991

Methods	Randomized, double blind Sample size at entry Acyclovir - 408 Placebo - 407
Participants	Country: USA Immunocompetent children with clinically diagnosed varicella Number enrolled: 815 Mean age: 5.18 years Sex: 365 males; 359 females Withdrawals: 41 acyclovir; 50 placebo
Interventions	Acyclovir 20 mg/kg four time/day for five days Placebo Patients enrolled within 24 hours of rash onset; text states that treatment started on day of enrolment
Outcomes	Maximum of lesions Number with > 500 lesions Residual lesions at day 28

Dunkle 1991 (*Continued*)

Notes	Quality score = three IMPUTATIONS Time to No New Lesions: summary measures imputed from scanned graph Maximum Number of Lesions: SD imputed from p-value Time to No Fever: summary measures imputed from scanned graph Time to No Itching: summary measures imputed from scanned graph

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Study	Reason for exclusion
Balfour 2001	No placebo group - all patients received acyclovir
Feder 1990	Not RCT
Huang 1995	Not RCT
Lin 1997	Not RCT
Suga 1993	Not RCT

DATA AND ANALYSES

Comparison 1. Acyclovir versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to no new lesions	3	888	Mean Difference (IV, Random, 95% CI)	-0.79 [-1.59, 0.02]
1.1 Age group (2 to 12)	1	724	Mean Difference (IV, Random, 95% CI)	-1.22 [-1.47, -0.97]
1.2 Age group (5 to 16)	1	102	Mean Difference (IV, Random, 95% CI)	Not estimable
1.3 Age group (13 to 18)	1	62	Mean Difference (IV, Random, 95% CI)	-1.13 [-1.75, -0.51]
2 Maximum number of lesions	3	888	Mean Difference (IV, Random, 95% CI)	-76.42 [-144.95, -7.90]
2.1 Age group (2 to 12)	1	724	Mean Difference (IV, Random, 95% CI)	-53.0 [-86.49, -19.51]
2.2 Age group (5 to 16)	1	102	Mean Difference (IV, Random, 95% CI)	-164.0 [-228.31, -99.69]
2.3 Age group (13 to 18)	1	62	Mean Difference (IV, Random, 95% CI)	-24.0 [-73.73, 25.73]
3 Time to no fever	3	856	Mean Difference (IV, Random, 95% CI)	-1.09 [-1.27, -0.92]
3.1 Age group (2 to 12)	1	724	Mean Difference (IV, Random, 95% CI)	-1.09 [-1.28, -0.90]
3.2 Age group (5 to 16)	1	79	Mean Difference (IV, Random, 95% CI)	-1.0 [-1.53, -0.47]
3.3 Age group (13 to 18)	1	53	Mean Difference (IV, Random, 95% CI)	-1.31 [-2.02, -0.60]
4 Time to no itching	2	826	Mean Difference (IV, Random, 95% CI)	-0.46 [-1.26, 0.34]
4.1 Age group (2 to 12)	1	724	Mean Difference (IV, Random, 95% CI)	-0.82 [-0.99, -0.65]
4.2 Age group (5 to 16)	1	102	Mean Difference (IV, Random, 95% CI)	Not estimable
5 Skin complications	3	888	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.19, 1.47]
5.1 Age group (2 to 12)	1	724	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.18, 2.28]
5.2 Age group (5 to 16)	1	62	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.03]
5.3 Age group (13 to 18)	1	102	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.31]
6 CNS complications	2	786	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.03, 3.12]
6.1 Age group (2 to 12)	1	724	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.93]
6.2 Age group (5 to 16)	1	62	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.88]
7 Respiratory complications	2	786	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.33, 3.06]
7.1 Age group (2 to 12)	1	724	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.11, 3.86]
7.2 Age group (5 to 16)	1	62	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.32, 5.47]

Analysis 1.1. Comparison 1 Acyclovir versus placebo, Outcome 1 Time to no new lesions.

Review: Acyclovir for treating varicella in otherwise healthy children and adolescents

Comparison: 1 Acyclovir versus placebo

Outcome: 1 Time to no new lesions

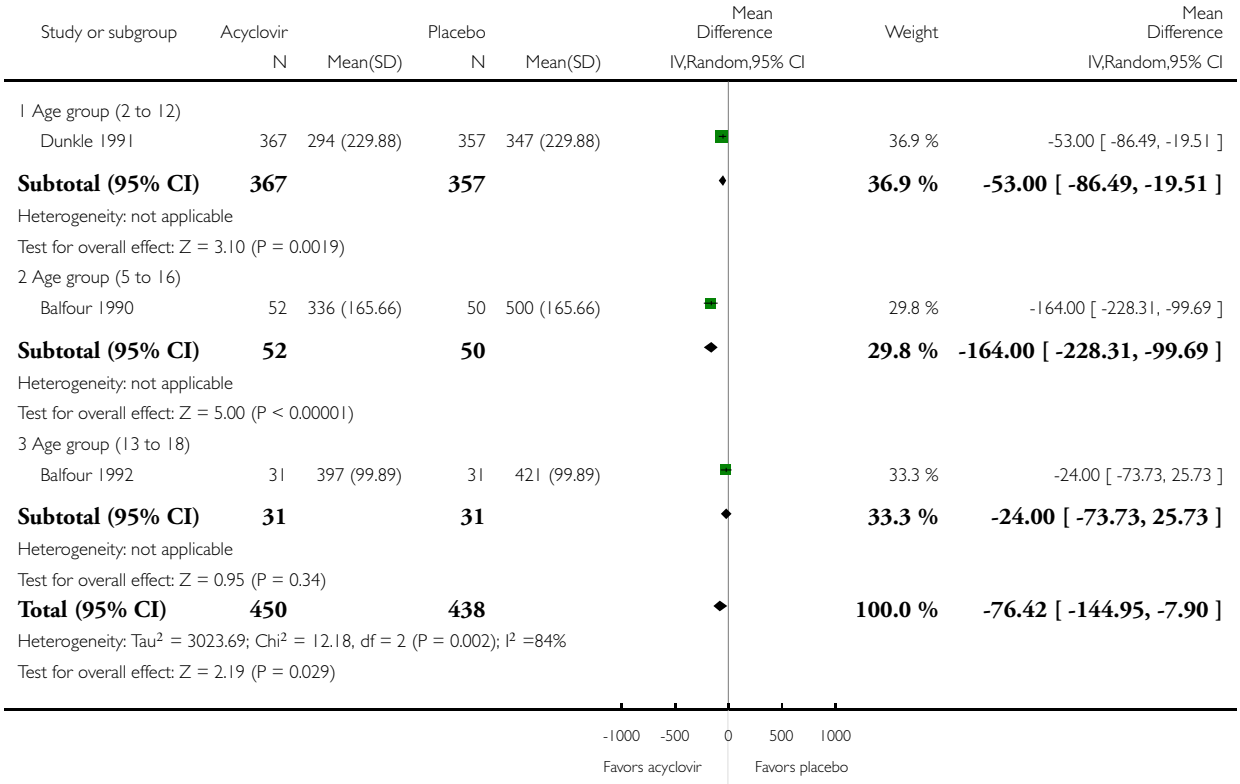
Study or subgroup	Acyclovir N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Age group (2 to 12)							
Dunkle 1991	367	1.76 (1.24)	357	2.98 (2.13)		36.0 %	-1.22 [-1.47, -0.97]
Subtotal (95% CI)	**367**		**357**			**36.0 %**	**-1.22 [-1.47, -0.97]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.39 (P < 0.00001)							
2 Age group (5 to 16)							
Balfour 1990	52	3 (1.18)	50	3 (1.18)		33.3 %	0.0 [-0.46, 0.46]
Subtotal (95% CI)	**52**		**50**			**33.3 %**	**0.0 [-0.46, 0.46]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
3 Age group (13 to 18)							
Balfour 1992	31	2.48 (0.98)	31	3.61 (1.45)		30.6 %	-1.13 [-1.75, -0.51]
Subtotal (95% CI)	**31**		**31**			**30.6 %**	**-1.13 [-1.75, -0.51]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.59 (P = 0.00032)							
Total (95% CI)	**450**		**438**			**100.0 %**	**-0.79 [-1.59, 0.02]**
Heterogeneity: Tau^2 = 0.45; Chi^2 = 21.16, df = 2 (P = 0.00003); I^2 =91%							
Test for overall effect: Z = 1.92 (P = 0.055)							

Analysis 1.2. Comparison 1 Acyclovir versus placebo, Outcome 2 Maximum number of lesions.

Review: Acyclovir for treating varicella in otherwise healthy children and adolescents

Comparison: 1 Acyclovir versus placebo

Outcome: 2 Maximum number of lesions



Analysis 1.3. Comparison 1 Acyclovir versus placebo, Outcome 3 Time to no fever.

Review: Acyclovir for treating varicella in otherwise healthy children and adolescents

Comparison: 1 Acyclovir versus placebo

Outcome: 3 Time to no fever

Study or subgroup	Acyclovir N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Age group (2 to 12)							
Dunkle 1991	367	1.43 (1.15)	357	2.52 (1.46)		83.0 %	-1.09 [-1.28, -0.90]
Subtotal (95% CI)	**367**		**357**			**83.0 %**	**-1.09 [-1.28, -0.90]**
Heterogeneity: not applicable							
Test for overall effect: Z = 11.14 (P < 0.00001)							
2 Age group (5 to 16)							
Balfour 1990	37	1 (1.19)	42	2 (1.19)		11.0 %	-1.00 [-1.53, -0.47]
Subtotal (95% CI)	**37**		**42**			**11.0 %**	**-1.00 [-1.53, -0.47]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.73 (P = 0.00019)							
3 Age group (13 to 18)							
Balfour 1992	25	1.28 (1.24)	28	2.59 (1.41)		6.0 %	-1.31 [-2.02, -0.60]
Subtotal (95% CI)	**25**		**28**			**6.0 %**	**-1.31 [-2.02, -0.60]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.60 (P = 0.00032)							
Total (95% CI)	**429**		**427**			**100.0 %**	**-1.09 [-1.27, -0.92]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.48, df = 2 (P = 0.79); I^2 =0.0%							
Test for overall effect: Z = 12.27 (P < 0.00001)							

Analysis 1.4. Comparison 1 Acyclovir versus placebo, Outcome 4 Time to no itching.

Review: Acyclovir for treating varicella in otherwise healthy children and adolescents

Comparison: 1 Acyclovir versus placebo

Outcome: 4 Time to no itching

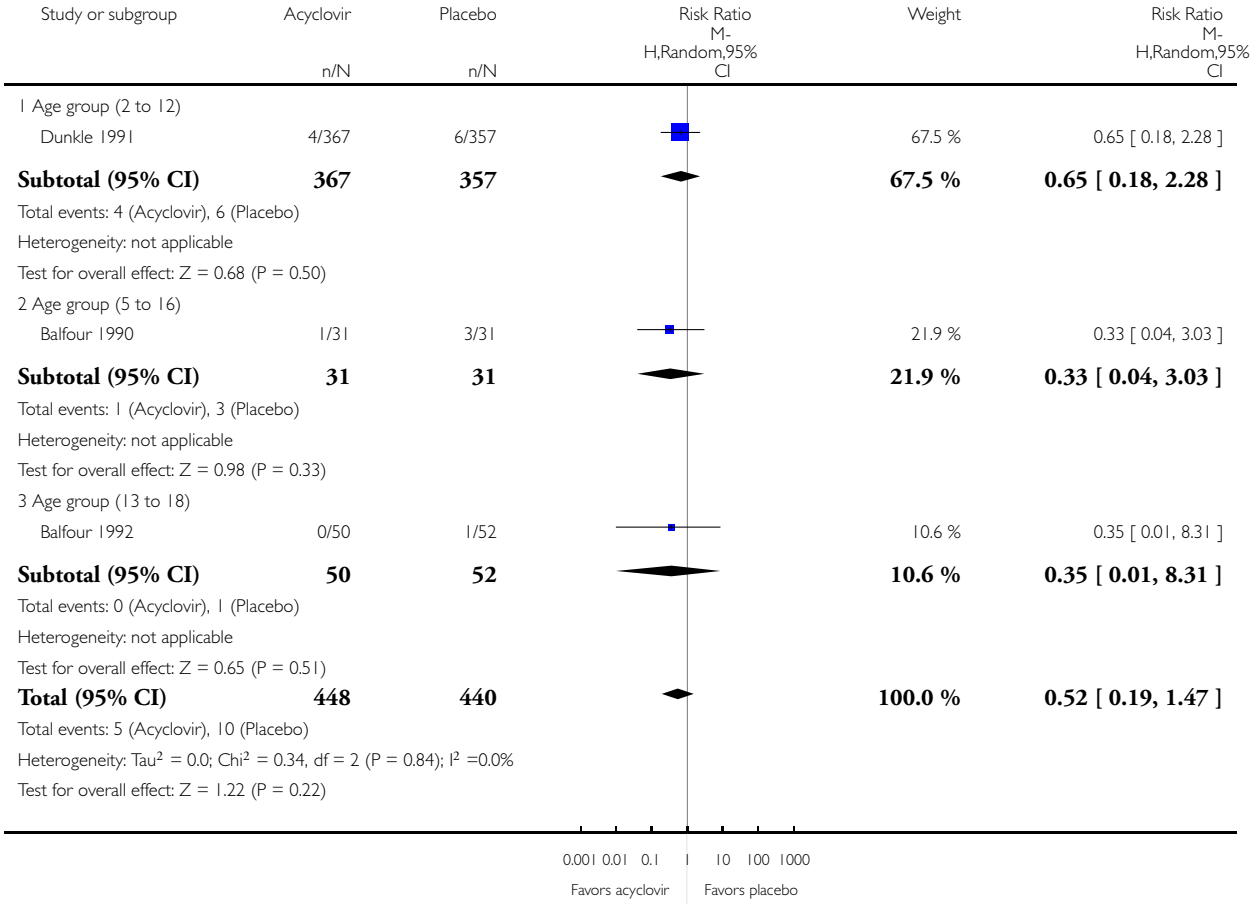
Study or subgroup	Acyclovir N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Age group (2 to 12)							
Dunkle 1991	367	1.91 (0.84)	357	2.73 (1.36)		55.9 %	-0.82 [-0.99, -0.65]
Subtotal (95% CI)	**367**		**357**			**55.9 %**	**-0.82 [-0.99, -0.65]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.73 (P < 0.00001)							
2 Age group (5 to 16)							
Balfour 1990	52	3 (1.48)	50	3 (1.48)		44.1 %	0.0 [-0.57, 0.57]
Subtotal (95% CI)	**52**		**50**			**44.1 %**	**0.0 [-0.57, 0.57]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Total (95% CI)	**419**		**407**			**100.0 %**	**-0.46 [-1.26, 0.34]**
Heterogeneity: Tau^2 = 0.29; Chi^2 = 7.23, df = 1 (P = 0.01); I^2 =86%							
Test for overall effect: Z = 1.12 (P = 0.26)							

Analysis 1.5. Comparison 1 Acyclovir versus placebo, Outcome 5 Skin complications.

Review: Acyclovir for treating varicella in otherwise healthy children and adolescents

Comparison: 1 Acyclovir versus placebo

Outcome: 5 Skin complications

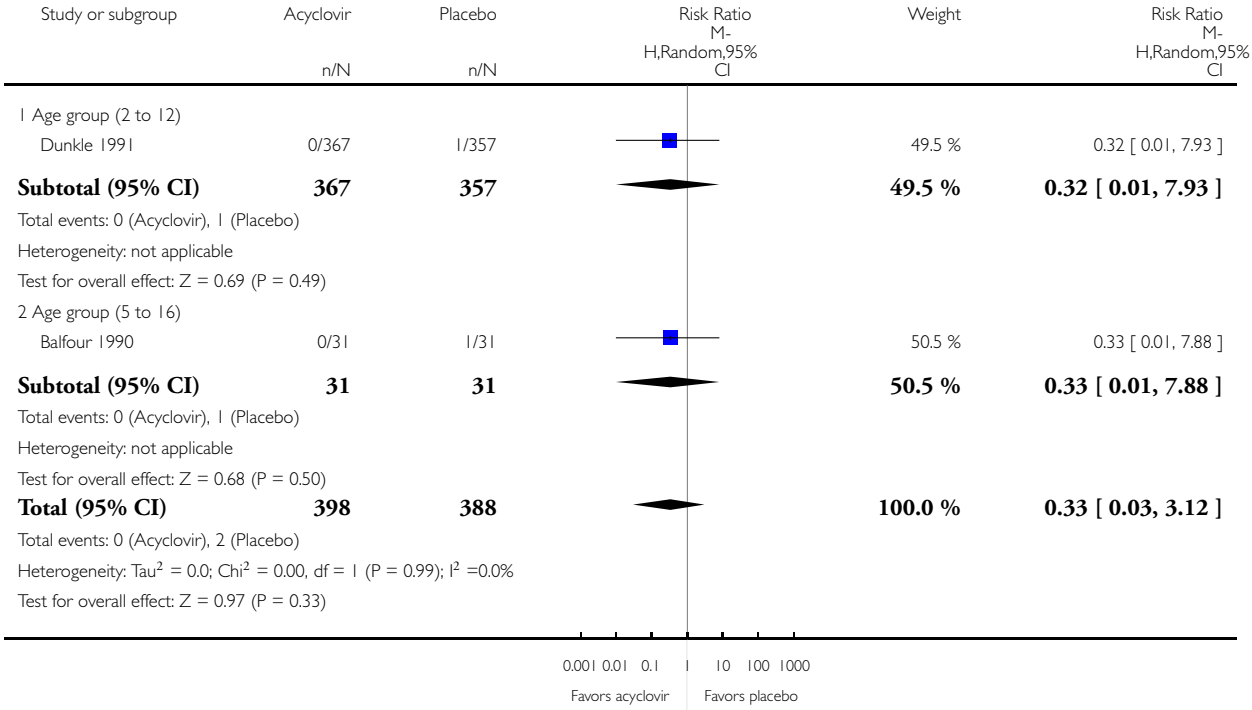


Analysis 1.6. Comparison 1 Acyclovir versus placebo, Outcome 6 CNS complications.

Review: Acyclovir for treating varicella in otherwise healthy children and adolescents

Comparison: 1 Acyclovir versus placebo

Outcome: 6 CNS complications

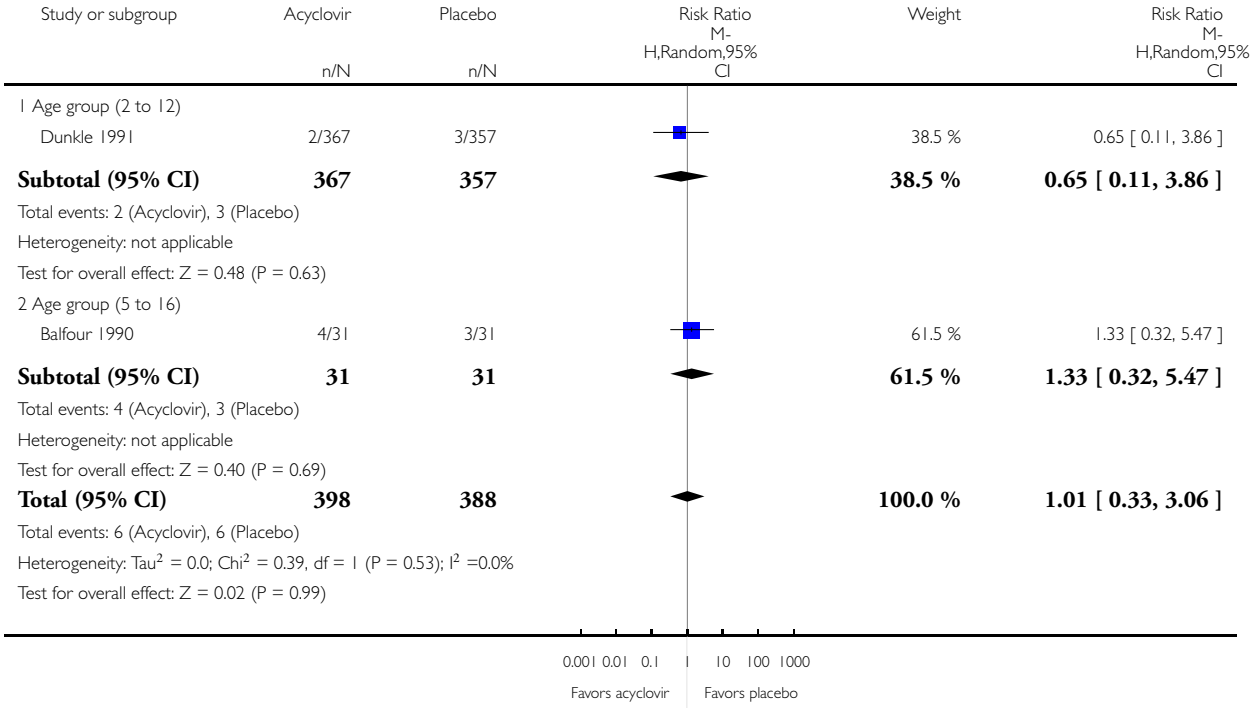


Analysis 1.7. Comparison 1 Acyclovir versus placebo, Outcome 7 Respiratory complications.

Review: Acyclovir for treating varicella in otherwise healthy children and adolescents

Comparison: 1 Acyclovir versus placebo

Outcome: 7 Respiratory complications



WHAT'S NEW

Last assessed as up-to-date: 27 September 2008.

Date	Event	Description
9 December 2010	Amended	Contact details updated.
28 September 2008	Review declared as stable	As there have been no new trials to include/exclude in the last two updates of this review, this review will not need any further updates. The review authors believe that the question is no longer relevant to current clinical practice

HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 4, 2002

Date	Event	Description
9 September 2010	Amended	Contact details updated.
16 June 2010	Amended	Contact details updated.
17 February 2010	Amended	Contact details updated.
21 January 2010	Amended	Contact details updated.
6 August 2009	Amended	Contact details updated.
28 September 2008	New search has been performed	In this update, we re-ran the electronic searches in September 2008 and found no new trials that met the inclusion criteria for the review
1 July 2008	Amended	Converted to new review format.
24 June 2005	New search has been performed	In this updated review for Issue 4, 2005, we re-ran the electronic searches in June 2005 and found no new trials that met the inclusion criteria for the review
29 May 2003	New citation required and conclusions have changed	A substantial change was made in this updated review published in *The Cochrane Library*, Issue 2, 2004. Significant heterogeneity exists between the trials. The reasons for this are not clear. The authors have pooled the results in this update, as is evident in the meta-analyses
30 September 2001	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

TPK conducted the quality assessment, provided overall methodological and clinical expertise, and contributed to the final manuscript.

LH assisted with searching and screening studies for inclusion, provided input on the analyses, and contributed to the final manuscript.

Both review authors read and approved the final manuscript.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

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External sources

- Children's Health Foundation of Northern Alberta, Canada.
- Alberta Heritage Foundation for Medical Research, Canada.

INDEX TERMS

Medical Subject Headings (MeSH)

Acyclovir [adverse effects; *therapeutic use]; Adolescent; Antiviral Agents [adverse effects; *therapeutic use]; Chickenpox [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Child; Child, Preschool; Humans