Adjuvant antiviral therapy for recurrent respiratory papillomatosis (Review)

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[Intervention Review]

Adjuvant antiviral therapy for recurrent respiratory papillomatosis

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ABSTRACT

Background

This is an update of a Cochrane Review originally published in Issue 4, 2005 of *The Cochrane Library* and previously updated in 2010.

Recurrent respiratory papillomatosis is a condition characterised by benign papillomatous (wart-like) growths in the upper airway. It can affect both adults and children causing airway obstruction and voice change. Treatment usually involves repeated surgical debulking of the papillomata. Several agents have been proposed as adjuvants to surgical debulking, including antivirals, administered systemically or injected into the lesions.

Objectives

To assess the effectiveness of antiviral agents as adjuvant therapy in the management of recurrent respiratory papillomatosis in children and adults.

Search methods

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the most recent search was 24 February 2012.

Selection criteria

Randomised controlled trials.

Data collection and analysis

We identified 143 references from the searches. Forty-three were appropriate for retrieval and assessed for eligibility by the authors. One randomised controlled trial met the inclusion criteria, involving 19 participants. We contacted the authors to obtain additional data to facilitate the review.

Main results

The included study was a single-institution, randomised, double-blind, placebo-controlled trial of intralesional cidofovir administered at the time of surgical debulking. Adults (n = 15) and children (n = 4) were included. We judged the study to have a reasonably low risk of bias. After a 12-month trial period, no difference was found between the cidofovir and placebo groups. Both groups showed a significant reduction in disease extent (as assessed at the time of surgery using the Derkay Scoring System), but no significant change in health-related quality of life.

Authors' conclusions

There is insufficient evidence to support the efficacy of antiviral agents as adjuvant therapy in the management of recurrent respiratory papillomatosis in children or adults. The included randomised controlled trial showed no advantage of intralesional cidofovir over placebo at 12 months. The study was limited by a small sample size and a change in the cidofovir concentration midway through the trial, from 0.3 mg/ml in children and 0.75 mg/ml in adults, to 5 mg/ml in both adults and children. An adequately powered randomised controlled trial of intra-lesional cidofovir, consistently using higher concentrations of cidofovir in comparison with injected placebo, would be required to determine effectiveness convincingly. Future studies must include health-related quality of life and symptom-based outcome measures.

PLAIN LANGUAGE SUMMARY

Antivirals for recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis (RRP) is a condition in which wart-like growths occur in the upper airway of children or adults. This can cause difficulty in breathing or a change in voice. This condition is usually treated by repeated surgery to remove these 'warts', but it has been proposed that additionally using antiviral medications may help this condition. This review found one good quality study of cidofovir (an antiviral agent) injected into the warts at the time of surgical removal. After one year of treatment, however, this study found no benefit of the injected cidofovir when compared to injected salt water solution (placebo). There is still a need for a larger randomised study which includes more patients, and higher doses of cidofovir.

BACKGROUND

This is an update of a Cochrane Review originally published in *The Cochrane Library* in Issue 4, 2005 and previously updated in 2010.

Recurrent respiratory papillomatosis (RRP) is a condition predominantly affecting the larynx and trachea (and occasionally bronchi and lung parenchyma). It is characterised by papillomatous (wart-like) growths in these areas. These papillomata may cause life-threatening airway obstruction or voice change (Derkay 2001). It is a potentially devastating disease with significant morbidity although it is rarely fatal. Although RRP is considered a benign condition, the papillomata are capable of undergoing a malignant transformation in 3% to 5% of patients (Kimberlin 2004). RRP has a bimodal age distribution, presenting commonly in children younger than five years or in adults between 20 and 30 years (Shykhon 2002). Incidence has previously been estimated as 4.3 per 100,000 per year in children and 1.8 per 100,000 in adults, based on a questionnaire of United States otolaryngologists (Derkay 1995). A population-level study of childhood RRP recently found an annual incidence of 0.24 per 100,000 per year across Canada (Campisi 2009).

The primary causative agent is human papilloma virus (HPV) (Gissman 1982), a small, non-enveloped, 20-sided, capsid virus with double-stranded circular DNA. The virus targets epithelial cells and can exist within its host in an active or latent form. HPV is the same virus associated with skin warts, genital condyloma and cervical cancer. Although around 90 different sub-types of human papilloma virus have been identified thus far (Menzo 2001), two sub-types are thought to cause the majority of RRP cases in patients, namely HPV-6 and HPV-11 (Corbitt 1988). Type 11 appears to be the more virulent of the two sub-types, associated with earlier presentation, longer disease activity, more surgical procedures, higher mortality rate, and more frequent malignant transformation (Rabah 2001). Co-infection of human papilloma virus with other viruses has been demonstrated (including herpes sim-

plex virus, cytomegalovirus and Epstein-Barr virus) and this can be predictive of an aggressive clinical course (Pou 1995). In juvenile-onset RRP, transmission may be secondary to direct contact with papillomata in an infected birth canal from maternal cervical human papilloma virus infection (Dillner 1999; Silverberg 2003). In the case of adult-onset RRP, modes of disease transmission have not been well established. Postulated mechanisms include activation of a latent virus present since birth, or infection acquired in adolescence or adult life as a result of oral or sexual contact (Kashima 1992).

The common symptoms of RRP include progressive hoarseness, stridor and respiratory distress. Less commonly RRP can present with a chronic cough, recurrent pneumonia, failure to thrive, dyspnoea and dysphagia (Derkay 2001). Diagnosis is made by visualisation with flexible nasolaryngoscopy or direct laryngo-bronchoscopy. Biopsy of the lesions is useful for histologic confirmation of RRP and to exclude malignant transformation. Derkay and Coltrera have established a staging system based upon area of involvement, severity of involvement and observational data such as the patient's voice quality and/or extent of respiratory distress (Derkay 1998). Inter-observer reliability has now been demonstrated for this staging system (Hester 2003). The primary purpose of this system is to standardise the evaluation of RRP patients so that established and emerging treatments can be evaluated.

The goals of therapy are to relieve airway obstruction, improve voice quality and facilitate remission. Treatment usually involves repeated surgical debulking of the papillomata under a general anaesthetic. Paediatric patients can need several procedures over many years. Several agents have been proposed as adjuvants to surgical debulking. These include antiviral agents, alpha-interferon, indole 3-carbinol and photodynamic therapy. A quadrivalent vaccine against HPV serotypes 6, 11, 16 and 18 offers the possibility of eventually reducing or eradicating this disease, but the long-term epidemiologic and economic impact of the vaccination on RRP will not be available for several years.

A variety of antiviral therapies have been used to treat RRP. These include systemically administered agents, such as aciclovir (formerly called acyclovir) and ribavirin, and others injected into the lesions, such as cidofovir. The mechanism of action of antiviral compounds is predominantly inhibition of viral nucleic acid synthesis. Direct action against the viruses involved in RRP is the likely mechanism for antiviral therapy efficacy. Various side effects have been associated with the use of available antiviral agents. These have included nausea, vomiting, abdominal pain, acute renal impairment, hepatitis and neutropenia (BNF 2003). A web-based survey in 2002 of American Society of Pediatric Otolaryngology members found that 10% of children with RRP were receiving adjuvant antiviral therapy, and 34 of 62 practices had tried using intra-lesional cidofovir (Schraff 2004). Similarly a postal survey of British Association of Paediatric Otolaryngology members in 2004 found five of 18 practices had used adjuvants, with 10% of RRP children treated with cidofovir (Tasca 2006). These surveys suggest antiviral adjuvant therapy may have been widely considered appropriate for some cases of RRP.

There have been no systematic reviews of the effectiveness and safety of using antivirals as adjuvant therapy in the treatment of RRP. Although an uncommon condition, RRP carries significant morbidity, and adjuvant antiviral therapy that has proven benefits could be usefully applied to this population. This review sets out to identify controlled evidence for using antivirals in RRP.

OBJECTIVES

To assess the efficacy of antiviral agents as adjuvant therapy in the management of recurrent respiratory papillomatosis in children and adults.

Therapeutic agents with antiviral properties but which are not themselves antiviral agents (e.g. alpha-interferon, vaccination, indole-3-carbinol) are not included in this review.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Patients of any age with recurrent respiratory papillomatosis.

Types of interventions

- Adjuvant systemic antiviral agent versus placebo or no adjuvant systemic antiviral agent.
- Adjuvant intra-lesional antiviral agent versus placebo or no adjuvant intra-lesional antiviral agent.

Types of outcome measures

Primary outcomes

- Improvement in symptoms, e.g. voice quality, respiratory distress, stridor or dyspnoea (validated subjective or objective measures are preferable; other measures will be assessed on an individual basis to ensure they do not incorporate an unacceptable risk of bias).

- Improvement in quality of life (validated quality of life measures are acceptable).

Secondary outcomes

- Reduction in mortality.
- Reduction in number and/or frequency of surgical interventions and/or time until first relapse requiring surgery.
- Reduction in number and/or duration of hospital stays.
- Reduction in volume of disease as assessed endoscopically.
- Adverse effects of antiviral agents.

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the last search was 24 February 2012, following previous searches in 2009, 2008 and 2004.

Electronic searches

We searched the following databases from their inception: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* Issue 2, 2012); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; ISRCTN; ClinicalTrials.gov; ICTRP; Google Scholar and Google.

We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011)). Search strategies for key databases including CENTRAL are shown in Appendix 1.

Searching other resources

For the 2012 and 2009 update searches, we scanned reference lists of identified studies for further trials. We searched PubMed, TRIPdatabase, *The Cochrane Library* and Google to retrieve existing systematic reviews potentially relevant to this systematic review, in order to search their reference lists for additional trials. Abstracts from conference proceedings were sought via the Cochrane Ear, Nose and Throat Disorders Group Trials Register. In previous searches we contacted leading experts in the field for information on any relevant unpublished data and we also contacted pharmaceutical companies manufacturing relevant antiviral agents to seek unpublished trial data.

Data collection and analysis

Data extraction and management

The authors independently extracted data from the studies using standardised data forms. The first author checked and entered data into the Cochrane Review Manager (RevMan) Version 5.1 computer software (RevMan 2011). Where necessary and where data from the study were not provided, we wrote to the authors of the study requesting further information.

Assessment of risk of bias in included studies

The authors reviewed the risk of bias of each trial independently. This was performed in accordance with the current recommended approach for assessing the risk of bias in Cochrane reviews using the Cochrane Collaboration's tool for assessing risk of bias (Handbook 2011). This included an assessment of the risk of bias from sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential threats to validity. The level of agreement between the two authors was recorded. We would have resolved any disagreements through discussion, or by contacting another person at the Cochrane Ear, Nose and Throat Disorders Group editorial base when necessary. Where required, we sought additional information from trial authors to clarify methodology.

Measures of treatment effect

We planned to analyse data on an intention-to-treat basis. Data from adults and children were to be analysed separately where possible. Where studies were of sufficient quality, we planned to combine data to give a summary measure of effect. Subgroup analyses were to be performed, where possible, to consider the effects of dose and duration of antiviral treatment, age, severity of disease and duration of disease.

RESULTS

Description of studies

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

The most recent searches in 2012 retrieved a total of 109 references, which reduced to 94 once duplicates were removed and a broad subject sift was conducted. We screened the 94 references but identified no further studies which met the inclusion criteria for the review.

From the 2009 update searches a total of 47 references were retrieved: 26 of these were removed in first-level screening (i.e. removal of duplicates and clearly irrelevant references), leaving 21 references for further consideration.

From previous searches we identified 140 potentially relevant articles. After reading the abstracts, we identified 43 articles specifically related to antivirals and recurrent respiratory papillomatosis (RRP). The other articles related to unrelated conditions, or other treatment modalities beyond the scope of this review.

We retrieved all the potentially relevant articles relating to RRP and antivirals in order to assess the papers for inclusion and to search the bibliography for further relevant trials fulfilling the inclusion criteria. The retrieved articles consisted of one randomised controlled trial (McMurray 2008), 15 review articles (including the original version of this Cochrane review), 24 uncontrolled trials or case series, one previously registered but unfinished study (Morrison 2003) and a further two unrelated articles. We searched reference lists from the articles and identified three further potentially relevant articles. These three articles were retrieved and were also found to be uncontrolled trials or case series. Correspondence with experts and authors in the field led to the identification of a conference abstract for an unpublished controlled study on ribavirin for RRP (Ostrow 1999). The author was unable to provide any details of this unpublished study for inclusion.

Included studies

The one identified randomised controlled trial was the only study to meet the inclusion criteria for this review (McMurray 2008).

Risk of bias in included studies

We assessed the risk of bias of the one included study (McMurray 2008) after additional unpublished data and study information were provided by the authors. We performed assessment of risk of bias in accordance with the current recommended approach, using the Cochrane Collaboration's tool for assessing risk of bias (Handbook 2011). The trial was of reasonable quality. The risk of bias assessment of this study is detailed below.

Allocation

Allocation was performed centrally (pharmaceutical research centre-controlled) and therefore participants and investigators could not foresee assignment. Participants were randomly assigned to either a cidofovir injection or a placebo injection according to a pre-determined random sequence stratified for adults versus children. The risk of allocation bias was low and the risk of a sequence generation bias was low.

Blinding

Both investigators and participants were blinded to the intervention, and a placebo control was employed. The placebo had a volume, colour and viscosity that was identical to the active drug. The risk of a blinding bias was therefore low.

Incomplete outcome data

There were no withdrawals and the authors provided outcome data missing from the published study. The risk of incomplete outcome data bias was therefore low.

Selective reporting

Neither the published study, nor the supplementary data provided by the authors, included all measured time points for all outcome measures in the study protocol. The risk of selective reporting bias is therefore unclear.

Other potential sources of bias

The concentration of cidofovir administered during the trial was dramatically increased midway through the study, from 0.3 mg/ml in children (less than 18 years of age) and 0.75 mg/ml in adults (18 years of age and older), to 5 mg/ml in both adults and children. It is unclear whether the participants and/or investigators were aware of the change in concentration during the study. Of 10 participants randomised to the intervention group, only three received the higher concentration of cidofovir. The study drugs and placebo were donated by a pharmaceutical company. The recruitment of children to the study was described as difficult and this limits the availability of data on children.

Effects of interventions

Nineteen patients were enrolled in the study, 10 receiving intra-lesional cidofovir versus nine receiving intra-lesional placebo. The Derkay Severity Score was significantly reduced from baseline at the two-month and 12-month follow-up assessments in both the cidofovir and the placebo groups. The higher the Derkay Severity Score, the more severe the disease state (Derkay 1998). At 12 months, the mean Derkay Severity Score was reduced from 13.2 to 2.7 in the cidofovir group, and from 12.0 to 5.1 in the placebo group. Median scores were not available. There was no statistically significant difference between the placebo and cidofovir groups (using a non-parametric tests) either pre-treatment or at 12 months.

Health-related quality of life was measured using the patient-reported Quality Metric Short Form 12 (Ware 1996), using two domains: the Mental Composite Score and the Physical Composite Score. These scores can range from 0 to 100 and lower scores represent a poorer perception of health quality. After 12 months,

mean Mental Composite Scores changed from 54.7 to 54.1 in the intervention group and from 48.8 to 56.0 in the placebo group. Mean Physical Composite Scores changed from 48.1 to 52.0 in the intervention group and from 55.2 to 53.6 in the placebo group. There was no significant difference between the study arms (using a non-parametric).

The voice-related quality of life was measured using the Vocal Handicap Index (Zur 2007), where scores range from 0 to 100 and increasing scores represent increasing perceived voice impairment. Data were not presented in the published study but were made available by the authors for this review for 18 patients (nine in each group). After 12 months, the cidofovir group scores improved from 68.3 to 31.9, and the placebo group scores improved from 64.4 to 42.7. The authors did not provide adequate data to allow comparison of the pre- and post- 12-month scores using a non-parametric paired statistical test. There were no differences in the 12-month scores. There was no significant difference between the study arms (using a non-parametric test).

There were too few paediatric patients recruited (four in total) to allow meaningful analysis of the Pediatric Quality of Life Inventory (Varni 1999) outcomes.

There was no difference between the placebo and intervention groups in the number of surgical procedures required over the 12-month study period (average three for both).

DISCUSSION

Summary of main results

One randomised controlled trial was identified for inclusion in this review. This study was not published at the time of the previous version of this review. This was a 12-month, double-blind, randomised controlled trial of intra-lesional cidofovir versus placebo (saline solution) at the time of any surgical procedures for papilloma debulking. The study included the primary outcome measures we sought in this review (quality of life and symptoms) as well as a measure of disease severity. When comparing the pre-treatment and 12-month follow-up outcomes, there were no significant differences between the intervention and placebo study arms. At 12 months, both arms showed a significant improvement in Derkay Severity Score, but neither showed a change in overall health-related quality of life. This suggests that the natural history is for an improvement in disease severity over time. Therefore, improvements previously attributed to intra-lesional cidofovir by other uncontrolled trials may be somewhat explained by the natural history of the disease. This confirms the importance of using a placebo control when testing this intervention. Another explanation is that the injection of a fluid volume into the papilloma (which occurred in both study groups) may have some impact on the disease outside any antiviral effect.

Also of note was the lack of an improvement in the quality of life measure to parallel the Derkay Severity Score improvement. This suggests that the Derkay Severity Score, an intra-operative observed measure of anatomical disease bulk, may have limitations in demonstrating disease severity, or that the quality of life measures may have inadequate sensitivity.

Overall completeness and applicability of evidence

We made efforts to identify all relevant studies and excluded no study due to language. The included randomised controlled trial was highly applicable, and remains the only available controlled study of antivirals for RRP. In the late 1990s, the US National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (CASG) had attempted to conduct a large, placebo-controlled investigation of intra-lesional cidofovir, but unfortunately the study was closed in 2000 due to poor accrual (Kimberlin 2004). It was suggested that recruitment for this study was unsuccessful because of constraints placed by the US Food and Drug Administration. The organisers were contacted but no data were available for inclusion in this review.

Quality of the evidence

The evidence available for the review was limited to one good quality randomised controlled trial. Allocation was performed centrally and therefore participants and investigators could not foresee assignment. Participants were randomly assigned to either a cidofovir injection or a placebo injection according to a pre-determined random sequence stratified for adults versus children. Both investigators and participants were blinded to the intervention, and a placebo control was employed. There were no withdrawals and the authors provided outcome data missing from the published study.

There are two main limitations with the included study: the small sample size which increases the chance of a type II error, and the change in intervention during the study (cidofovir concentration of cidofovir from 0.3 mg/ml in children and 0.75 mg/ml in adults, to 5 mg/ml in both adults and children).

Potential biases in the review process

The authors reviewed the risk of bias of the trial independently and in accordance with the current recommended approach for assessing the risk of bias in Cochrane reviews (Handbook 2011). There was therefore a low risk of bias in the review process, and the authors have no conflicts of interest.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence from randomised controlled trials to support the efficacy of antiviral agents as adjuvant therapy in the management of recurrent respiratory papillomatosis in children or adults. The included randomised controlled trial showed an improvement in disease appearance (Derkay Severity Score) in both the placebo and intra-lesional cidofovir groups at 12 months. The improvement may therefore have been related to the natural history of the disease or the injection of a fluid volume itself. Quality of life did not improve in either group.

Implications for research

To determine whether intra-lesional cidofovir has efficacy there is a need for further well-designed, randomised, placebo-controlled trials with appropriate sample size and drug concentrations. As the condition is relatively uncommon, it is likely that a multi-centre trial will be required for adequate patient numbers to obtain appropriate study power. Long-term follow up will be required to assess the impact of these treatments and potential complications sufficiently. The included randomised controlled study exemplified the importance of using a control group in assessing interventions in this condition. Future studies must include health-related quality of life and symptom-based outcome measures.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

McMurray 2008

Methods	Randomised, double-blind, placebo-controlled trial of intra-lesional injection of cidofovir versus intra-lesional injection of placebo (saline solution) at the time of any surgical procedures for papilloma debulking, over a 12-month time period
Participants	19 participants; 10 randomised to treatment (2 children) and 9 to placebo (2 children)
Interventions	All patients received surgical debulking of their papilloma as required, with either the carbon dioxide laser ablation or microresection using a powered instrument (choice determined by surgeon's preference). After completion of papilloma debulking, the surgeon then infiltrated the placebo or cidofovir into the tumour base. The concentration of cidofovir administered was initially 0.3 mg/ml in children and 0.75 mg/ml in adults, and midway through the study was increased to 5 mg/ml in both adults and children. The number of injections per treatment and the volume of each injection was at the surgeons' discretion
Outcomes	Derkay Severity Score (Derkay 1998), Quality Metric Short Form 12 (Ware 1996), Pediatric Quality of Life Inventory (Varni 1999)
Notes	Details of the number of injections and volumes of injections for the 2 groups were not available, but were described as not significantly different between the groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation of was performed centrally (pharmaceutical research centre-controlled) and therefore participants and investigators could not foresee assignment
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned to either a cidofovir injection or placebo injection according to a pre-determined random sequence stratified for adults versus children
Blinding (performance bias and detection bias) All outcomes	Low risk	Both investigators and participants were blinded to the intervention, and a placebo control was employed. The placebo had a volume, colour and viscosity that was identical to the active drug

Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no withdrawals and the authors provided outcome data missing from the published study
Selective reporting (reporting bias)	Unclear risk	Neither the published study, nor the supplementary data provided by the authors, included all measured time points for all outcome measures in the study protocol
Other bias	Unclear risk	The concentration of cidofovir administered during the trial was dramatically increased midway through the study, from 0.3 mg/ml in children and 0.75 mg/ml in adults, to 5 mg/ml in both adults and children. It is unclear whether the participants and/or investigators were aware of the change in concentration during the study. Of 10 participants randomised to the intervention group, only 3 received the higher concentration of cidofovir. The study drugs and placebo were donated by a pharmaceutical company. The recruitment of children to the study was described as difficult and this limits the availability of data on children

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

Study	Reason for exclusion
Morrison 2003	Uncompleted study. Author has been contacted and there are no unpublished data available
Ostrow 1999	Information is only available from the brief conference presentation abstract. Author has been contacted and is unable to provide any data or information related to study

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Search strategies

CENTRAL	PubMed	EMBASE (Ovid)
1. PAPILLOMA explode all trees (MeSH) 2. PAPILLOMAVIRUS INFECTIONS explode all trees (MeSH) 3. (PAPILLOMA* OR WART* OR HPV ADJ VIRUS) 4. #1 OR #2 OR #3 5. (LARYN* OR TRACHE* OR PHARYN* OR VOCAL ADJ CORD* OR VOCAL ADJ FOLD* OR VOICE ADJ BOX OR THROAT OR RESPIRAT* OR SQUAMOUS ADJ CELL OR LARYNGOTRACHEOBRONCHIAL OR UPPER ADJ AIRWAY* OR BRONCHIAL) 6. #4 AND #5 7. (LARYNGEAL ADJ PAPILLOMA* OR RECURRENT NEAR PAPILLOMA* OR RRP OR JORRP OR AORRP) 8. #6 OR #7 9. ANTIVIRAL AGENTS explode all trees (MeSH) 10. ANTINEOPLASTIC AGENTS [tu] explode all trees (MeSH) 11. RESPIRATORY TRACT NEOPLASMS [dt] single term (MeSH) 12. LARYNGEAL NEOPLASMS [dt] single term (MeSH) 13. BRONCHIAL NEOPLASMS [dt] single term (MeSH) 14. TRACHEAL NEOPLASMS [dt] single term (MeSH) 15. AIRWAY OBSTRUCTION [dt] single term (MeSH) 16. CYTOSINE single term (MeSH) 17. RIBAVIRIN single term (MeSH)	(((((“Papilloma”[Mesh]) OR (“Papillomavirus Infections”[Mesh]) OR (PAPILLOMA* OR WART* OR “HPV VIRUS”)) AND ((LARYN* OR TRACHE* OR PHARYN* OR THROAT OR RESPIRAT* OR “SQUAMOUS CELL” OR LARYNGOTRACHEOBRONCHIAL OR BRONCHIAL) OR ((VOCAL OR Voice) AND (CORD OR FOLD* OR VOICE OR BOX)) OR (upper AND airway*))) OR (LARYNGEAL AND PAPILLOMA*) OR (RECURRENT AND PAPILLOMA*) OR (RRP OR JORRP OR AORRP)) AND (“Antiviral Agents”[Mesh]) OR (“Antineoplastic Agents/therapeutic use”[Mesh]) OR (“Respiratory Tract Neoplasms/drug therapy”[Mesh]) OR (“Laryngeal Neoplasms/drug therapy”[Mesh]) OR (“Bronchial Neoplasms/drug therapy”[Mesh]) OR (“tracheal Neoplasms/drug therapy”[Mesh]) OR (“airway obstruction/drug therapy”[Mesh]) OR (“CYTOSINE”[Mesh]) OR (“RIBAVIRIN”[Mesh]) OR (ANTIVIRAL* OR ANTIVIROTIC OR VIRUCI* OR VIROSTATIC OR VIRUSTATIC OR VIRUS AND REPRESSOR* OR VIRUS AND INHIBIT* OR DESTROY* AND VIRUS* OR ANTI AND VIRAL*) OR (CIDOFOVIR OR RIBAVIRIN OR ACYCLOVIR OR ACICLOVIR OR FLUMIDINUL)))	1 exp PAPILLOMA/ or exp papilloma virus/ or papillomatosis/ or larynx papillomatosis/ 2 (PAPILLOMA* or WART* or (HPV adj VIRUS)).tw. 3 1 or 2 4 exp larynx/ 5 (LARYN* or PHARYN* or TRACHE* or (VOCAL adj CORD*) or (VOCAL adj FOLD*) or (VOICE adj BOX) or THROAT or RESPIRAT* or (SQUAMOUS adj CELL) or LARYNGOTRACHEOBRONCHIAL or (UPPER adj AIRWAY*) or BRONCHIAL).tw. 6 4 or 5 7 6 and 3 8 ((LARYNGEAL adj PAPILLOMA*) or (RECURRENT and PAPILLOMA*) or RRP or JORPP or AORRP).tw. 9 8 or 7 10 exp Antivirus agent/ or antiviral activity/ 11 exp respiratory tract tumor/dt [Drug Therapy] 12 exp airway obstruction/dt [Drug Therapy] 13 (ANTIVIRAL* or (ANTI adj VIRAL*) or ANTIVIROTIC or VIRUCI* or VIROSTATIC or VIRUSTATIC or (VIRUS adj REPRESSOR*) or (VIRUS adj INHIBIT*) or (DESTROY* and VIRUS*) or CIDOFOVIR or RIBAVIRIN or ACYCLOVIR or ACICLOVIR or FLUMIDINUL).tw. 14 11 or 13 or 10 or 12

(*Continued*)

18. ACYCLOVIR explode all trees (MeSH) 19. (ANTIVIRAL* OR ANTI ADJ VIRAL* OR ANTIVIROTIC OR VIRUCI* OR VIROSTATIC OR VIRUSTATIC OR VIRUS ADJ REPRESSOR* OR VIRUS ADJ INHIBIT* OR DESTROY* NEAR VIRUS*) 20. (CIDOFOVIR OR RIBAVIRIN OR ACYCLOVIR OR ACICLOVIR OR FLUMIDINUL) 21. #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR # 18 OR #19 OR #20 22. #8 AND #21		15 9 and 14
Web of Science/BIOSIS Previews (Web of Knowledge)	**CAB Abstracts (Ovid)**	**ISRCTN**
#1 TS=(LARYN* or PHARYN* or TRACHE* or (VOCAL adj CORD*) or (VOCAL adj FOLD*) or (VOICE adj BOX) or THROAT or RESPIRAT* or (SQUAMOUS adj CELL) or LARYNGOTRACHEOBRONCHIAL or (UPPER adj AIRWAY*) or BRONCHIAL) #2 TS=(PAPILLOMA* or WART* or (HPV adj VIRUS)) #3 #2 AND #1 # 4 TS=((LARYNGEAL adj PAPILLOMA*) or (RECURRENT and PAPILLOMA*) or RRP or JORPP or AORRP) #5 #4 OR #3 #6 TS=(ANTIVIRAL* or (ANTI adj VIRAL*) or ANTIVIROTIC or VIRUCI* or VIROSTATIC or VIRUSTATIC or (VIRUS adj REPRESSOR*) or (VIRUS adj INHIBIT*) or (DESTROY* and VIRUS*) or CIDOFOVIR or RIBAVIRIN or ACYCLOVIR or ACICLOVIR or FLUMIDINUL) #7 #5 AND #6	1 exp PAPILLOMA/ or exp papilloma virus/ or papillomatosis/ or larynx papillomatosis/ 2 (PAPILLOMA* or WART* or (HPV adj VIRUS)).tw. 3 1 or 2 4 exp larynx/ 5 (LARYN* or PHARYN* or TRACHE* or (VOCAL adj CORD*) or (VOCAL adj FOLD*) or (VOICE adj BOX) or THROAT or RESPIRAT* or (SQUAMOUS adj CELL) or LARYNGOTRACHEOBRONCHIAL or (UPPER adj AIRWAY*) or BRONCHIAL).tw. 6 4 or 5 7 6 and 3 8 ((LARYNGEAL adj PAPILLOMA*) or (RECURRENT and PAPILLOMA*) or RRP or JORPP or AORRP).tw. 9 8 or 7 10 (ANTIVIRAL* or (ANTI adj VIRAL*) or ANTIVIROTIC or VIRUCI* or VIROSTATIC or VIRUSTATIC or (VIRUS adj REPRESSOR*) or (VIRUS adj INHIBIT*) or (DESTROY* and VIRUS*) or CIDOFOVIR or RIBAVIRIN or ACYCLOVIR or ACICLOVIR or FLUMIDINUL).tw. 11 9 AND 10	(LARYN% OR PHARYN% OR TRACHE% OR VOCAL OR VOICE OR THROAT OR RESPIRAT%) AND (papilloma% OR wart% OR hpv)

WHAT'S NEW

Last assessed as up-to-date: 24 February 2012.

Date	Event	Description
25 October 2012	New citation required but conclusions have not changed	No new studies identified. Review conclusions remain unchanged
24 February 2012	New search has been performed	New searches run. We screened 94 references but identified no studies which met our inclusion criteria

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 4, 2005

Date	Event	Description
30 September 2009	New citation required and conclusions have changed	Updated review with new included study; conclusions changed.
25 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

NC searched for data, assessed quality of studies and wrote the review.

AJ independently assessed quality of studies and edited the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Airway Obstruction [drug therapy; virology]; Antiviral Agents [*therapeutic use]; Chemotherapy, Adjuvant; Cytosine [*analogs & derivatives; therapeutic use]; Papilloma [*drug therapy; surgery; virology]; Phosphonic Acids [*therapeutic use]; Recurrence; Respiratory Tract Neoplasms [*drug therapy; surgery; virology]

MeSH check words

Adolescent; Adult; Child; Humans