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Oral *Astragalus* (Huang qi) for preventing frequent episodes of acute respiratory tract infection in children.
Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD011958.
DOI: [10.1002/14651858.CD011958.pub2](https://doi.org/10.1002/14651858.CD011958.pub2).

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Oral *Astragalus* (Huang qi) for preventing frequent episodes of acute respiratory tract infection in children (Review)

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[Intervention Review]

Oral *Astragalus* (Huang qi) for preventing frequent episodes of acute respiratory tract infection in children

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Editorial group: Cochrane Acute Respiratory Infections Group.

Publication status and date: New, published in Issue 12, 2016.

Citation: Su G, Chen X, Liu Z, Yang L, Zhang L, Stålsby Lundborg C, Wen Z, Guo X, Qin X, Liang J, Liu X. Oral *Astragalus* (Huang qi) for preventing frequent episodes of acute respiratory tract infection in children. *Cochrane Database of Systematic Reviews* 2016, Issue 12. Art. No.: CD011958. DOI: [10.1002/14651858.CD011958.pub2](https://doi.org/10.1002/14651858.CD011958.pub2).

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ABSTRACT

Background

Acute respiratory tract infections (ARTIs) are common in children and can involve both upper and lower airways. Many children experience frequent ARTI episodes or recurrent respiratory tract infections (RRTIs) in early life, which creates challenges for paediatricians, primary care physicians, parents and carers of children.

In China, *Astragalus* (Huang qi), alone or in combination with other herbs, is used by Traditional Chinese Medicine (TCM) practitioners in the form of a water extract, to reduce the risk of ARTIs; it is believed to stimulate the immune system. Better understanding of the therapeutic mechanisms of *Astragalus* may provide insights into ARTI prevention, and consequently reduced antibiotic use.

Objectives

To assess the effectiveness and safety of oral *Astragalus* for preventing frequent episodes of acute respiratory tract infections (ARTIs) in children in community settings.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 12, 2015), MEDLINE (Ovid) (1946 to 31 December 2015), Embase (Elsevier) (1974 to 31 December 2015), AMED (Ovid) (1985 to 31 December 2015), Chinese National Knowledge Infrastructure (CNKI) (1979 to 31 December 2015) and Chinese Scientific Journals full text database (CQVIP) (1989 to 31 December 2015), China Biology Medicine disc (CBM 1976 to 31 December 2015) and Wanfang Data Knowledge Service Platform (WanFang) (1998 to 31 December 2015).

Selection criteria

We included randomised controlled trials (RCTs) comparing oral *Astragalus* as a sole Chinese herbal preparation with placebo to prevent frequent episodes of ARTIs in children.

Data collection and analysis

We used standard Cochrane methodological procedures for this review. We assessed search results to identify relevant studies. We planned to extract data using standardised forms. Disagreements were to be resolved through discussion. Risk of bias was to be assessed using the Cochrane 'Risk of bias' tool. We planned to use mean difference (MD) or standardised mean difference (SMD) for continuous data and risk ratio (RR) or odds ratio (OR) to analyse dichotomous data, both with 95% confidence intervals (CIs).

Main results

We identified 6080 records: 3352 from English language databases, 2724 from Chinese databases, and four from other sources. Following initial screening and deduplication, we obtained 120 full-text papers for assessment. Of these, 21 were not RCTs; 55 did not meet the inclusion criteria because: participants were aged over 14 years; definition was not included for recurrent or frequent episodes; *Astragalus* preparation was not an intervention; *Astragalus* preparation was in the formula but was not the sole agent; the *Astragalus* preparation was not administered orally; or *Astragalus* was used for treatment rather than prevention of ARTI. A further 44 studies were excluded because they were not placebo-controlled, although other inclusion criteria were fulfilled.

No RCTs met our inclusion criteria.

Authors' conclusions

We found insufficient evidence to enable assessment of the effectiveness and safety of oral *Astragalus* as a sole intervention to prevent frequent ARTIs in children aged up to 14 years.

PLAIN LANGUAGE SUMMARY

Can oral *Astragalus* (Huang qi) prevent frequent acute respiratory tract infections in children?

Review question

We assessed evidence for the benefits and harms of oral *Astragalus* used alone to prevent frequent episodes of acute respiratory infections (ARTIs) in children aged up to 14 years, compared to a dummy treatment. ARTIs include colds, sore throats, laryngitis, influenza, bronchitis and pneumonia.

Background

Many therapies are used to prevent ARTIs, especially in children. *Astragalus*, is a widely used and available herbal therapy that has been used for thousands of years in China to help prevent ARTIs. It is thought to boost immunity. Almost one in five children experience frequent ARTIs and treatment accounts for up to 75% of all prescribed antibiotics for children. Because most ARTIs are caused by viruses, antibiotics are not effective in treating these illnesses.

Search date

We searched the literature up to 31 December 2015.

Study characteristics

We identified 6080 potentially relevant records. After removing duplicate records, and those that did not meet our inclusion criteria, we obtained 120 full-text studies. We carefully assessed these studies for possible inclusion. We excluded most studies because: they presented unclear diagnosis criteria; *Astragalus* preparation was used with other agents; or *Astragalus* was not compared with a dummy treatment. No studies met our inclusion criteria and so we were unable to analyse any results.

Study funding sources

We could not assess study funding sources.

Key results

We did not find any studies that compared use of oral *Astragalus* alone with a dummy treatment to prevent frequent episodes of ARTI in children aged up to 14 years. Well-designed, conducted and reported studies investigating this issue are needed to enable assessment in the future.

Quality of the evidence

We could not assess evidence quality.

BACKGROUND

Description of the condition

Acute respiratory tract infection (ARTI) is a frequent childhood illness that can involve both upper and lower airways (WHO 1998). ARTIs include common cold, influenza, otitis media, sinusitis, tonsillitis, laryngitis, pharyngitis, bronchitis and pneumonia (CPSCMA 1999). Symptoms include nasal congestion and discharge, sneezing, sore throat, cough, sputum production, shortness of breath, chest pain and fever. Managing ARTIs is a continuing challenge for paediatricians and primary care physicians (CPSCMA 1999; Heikkinen 2003).

On average, children aged under two years experience about six common colds each year (Kvaerner 2000; Leder 2003; Monto 1993; Monto 2002), and healthy children under six years of age may experience up to five respiratory tract infections annually (Griffin 2004). A cohort study observed the history of respiratory infections among children living in urban areas in Germany, and indicated that the mean cumulative number of ARTIs in the first 12 years of life was 21.90 ± 9.00 episodes (Grüber 2008). In high-income countries, up to 25% of children aged up to one year, and 18% of children between the ages of one and four years, experience frequent ARTI episodes or RRTIs (Bellanti 1997); these are characterised as recurrent airway inflammation caused by infectious agents (Martino 2007).

In China, the definition of 'frequency' is based on age and disease type in accordance with Chinese guidelines (CPSCMA 2008; Table 1). This definition was developed by the respiratory group of the Paediatrics Committee Chinese Medical Association in 1988 (Hu 1988) and updated in 2007 (CPSCMA 2008). All criteria emphasise infection frequency and requires the absence of underlying pathological conditions such as primary or secondary immunodeficiency, cystic fibrosis, airway malformations or immotile-cilia syndrome.

Although factors influencing the aetiology of ARTIs are not always readily identifiable, viral agents are typically responsible for infection. Over 200 different viruses have been associated with ARTIs (Mäkelä 1998). Consequently, vaccination is theoretically an effective way to prevent some ARTIs in children; however, the high frequency of genetic exchange among different strains or subtypes, and high rates of nucleotide substitution, increase the difficulty of developing vaccines that remain persistently effective (Brichacek 1996; O'Brien 1995).

Description of the intervention

There are a number of non-specific preventative strategies for children with frequent ARTI episodes: general hygiene methods (Martino 2007); physical interventions (Jefferson 2009); administration of vitamin A and zinc (Kartasurya 2012), vitamin C (Hemilä 2013), or vitamin D supplements (Jolliffe 2013); probiotics (Hao 2015); homeopathic medicines (Steinsbekk 2005a; Steinsbekk 2005b); and immunostimulants (Del-Rio-Navarro 2012).

Traditional Chinese Medicine (TCM) follows a theoretical and methodological pathway, that differs from Western medicine, to assess cause, diagnosis and treatment. TCM may give new insight into preventive measures for children with frequent ARTI episodes. A main TCM treatment principle is to strengthen the Zheng Qi (a concept of the body's ability to self-regulate, pathogen resistance and self-recovery) and eliminate Evil Qi (pathogens).

This emphasises the importance of immune system functioning of patients and assumes that strengthening patients' immune systems might prevent and control infections. Certain herbs have been found to affect the distribution and expression of cytokines and their receptors in the immune system (Patwardhan 2005). *Astragalus* (Huang qi), a herb widely used to strengthen Qi, is widely available in supermarkets in China. For many centuries, *Astragalus*, alone or in combination with other herbs, has been used by TCM practitioners in the form of a water extract to prevent respiratory infections and to correct a condition called 'Qi deficiency', which typically includes symptoms such as: feelings of weakness, fatigue, apathy, poor appetite and vulnerability to respiratory infections (WHO 2007). In daily clinical TCM practice, there are different routes of administration, such as injection, self-made oral water extraction, oral liquid and oral granules. The dosage or equivalent of raw *Astragalus* varies from 10 g/day to 20 g/day and is adjusted according to age. In this review, we focused on all kinds of oral *Astragalus* preparations, however, we did not include parenteral preparations due to their limited use in children for ARTIs.

How the intervention might work

A study has suggested that *Astragalus* confers some immune-stimulating effects, including promoting white blood cell production, accelerating peripheral blood mononuclear cells and cytokine proliferation (Wang 2002). Hou 1981 found that healthy people who received oral *Astragalus* (8 g per day) for two months experienced significant improvement in the interferon-inducing ability of blood cells compared with control group participants. Two months after therapy ceased, the interferon-inducing ability remained significantly higher in the *Astragalus* group. In another study, *Astragalus* extract was prescribed to healthy adults for 20 consecutive days and increases were observed in immune parameters such as immunoglobulin (Ig) M, IgE and cyclic adenosine monophosphate (IBMSCAMS 1979). Nie 2009b demonstrated that *Astragalus* could decrease soluble interleukin-2 receptor (sIL-2R) and interleukin-8 levels, while increasing IgA, IgM and IgG levels in patients experiencing recurrent upper respiratory tract infections (URTIs). Based on these findings, *Astragalus* may have a biological basis for use in preventing ARTIs in children.

Why it is important to do this review

ARTIs in children impose significant social and financial burdens, particularly when parental time off work is considered, in addition to healthcare costs (Fendrick 2003; Hollinghurst 2008). A third of children in the USA and UK visit primary care physicians for ARTIs or related symptoms each year (Fendrick 2003; Hay 2005). Up to 75% of all antibiotics prescribed for children are for ARTIs, despite their mainly viral aetiology (Doan 2012). Overuse of antibiotics for children in primary care can induce bacterial resistance (Costelloe 2010), which may result in medicalisation of illness whereby patients are more likely to consult when similar symptoms recur – creating a cycle that exacerbates inappropriate use of antibiotics (Andrews 2012). Despite being mostly self-limiting illnesses, ARTIs remain a common cause of hospitalisation for children in high-income countries, and a major cause of death in low-income countries (Culebras 2013). Consequently, there are many social, financial and health reasons for preventing ARTI. Complementary and alternative medicine interventions may provide novel and efficient solutions.

Until the early nineteenth century in China, only TCM was practiced, and consequently it played an important role in healthcare. The popularity of TCM practice is increasing outside of China. According to recent national survey data, 60% to 75% of populations in Singapore, Japan, Taiwan and Korea consult TCM practitioners at least once per year (Cheung 2011). The USA is now the second largest consumer of TCM products (after China) where expenditure in 2010 was USD 7.6 billion (Cheung 2011). This indicates that interest in the potential of herbal treatments is widespread. The potential impact on public health is unknown, but could be substantial, given that herbal products can be purchased at pharmacies, supermarkets and health food stores.

Astragalus is a herb, extensively used both in clinical practice and as a food supplement in daily life in China. Although it is widely used to prevent ARTI in children who experience frequent episodes, no definitive conclusions about its effectiveness have been determined. Safety is an important concern, especially in the context of medications for children. Allergic reactions to *Astragalus* injections have been reported, and the safety of oral *Astragalus* preparation remains unclear (Fu 2009; Hu 2008; Xiong 2002).

Six Cochrane Reviews relate to herbal medicine and ARTI (Del-Rio-Navarro 2012; Huang 2012b; Jiang 2012; Jiang 2013; Liu 2012; Wu 2007); however, none focus on oral *Astragalus* for ARTI in children. Four of these reviews focused on the therapeutic effect of *Astragalus* rather than its prophylactic potential, or in reducing ARTI incidence (Huang 2012b; Jiang 2012; Liu 2012; Wu 2007). Del-Rio-Navarro 2012 focused on preventing respiratory tract infection in children, but the intervention was not related to *Astragalus*.

Our aim was to assess the effectiveness and safety of *Astragalus* for preventing frequent ARTIs in children in community settings, where *Astragalus* preparations were used as sole oral agents. We planned to assess ARTI frequency during the study period as the primary outcome.

OBJECTIVES

To assess the effectiveness and safety of oral *Astragalus* for preventing frequent episodes of acute respiratory tract infections (ARTIs) in children in community settings.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that compared oral *Astragalus* prescription as a sole Chinese herbal preparation, with placebo, to prevent frequent episodes of acute respiratory tract infection (ARTI) in children. We did not include trials in which *Astragalus* was one of multiple components in Traditional Chinese Medicine (TCM), such as Yupingfeng, BuZhongYiQiTang, etc.

Types of participants

We included children aged up to 14 years (without chronic disease) who experienced frequent ARTIs and were in community settings.

Frequency was defined in accordance with the current Chinese guideline (CPSCMA 2008; Table 1). We excluded trials that included participants who had asthma, asthmatic bronchitis, allergy and atopy, recurrent spastic laryngitis, tuberculosis,

idiopathic pulmonary haemosiderosis, bronchiolitis obliterans with organising pneumonia, eosinophilic pneumonia, sequoiosis or idiopathic interstitial pneumonia.

Types of interventions

1. *Astragalus* preparation as the sole agent, administered orally. We excluded formulas with multiple herbs even if they included *Astragalus*.
2. *Astragalus* preparation prescribed alone or as an adjunct for at least four weeks. Adjunctive treatment was only relevant if *Astragalus* could be isolated as the intervention: concurrent treatment was permitted, such as additional symptomatic treatment, but this needed to follow guidelines, and needed to be the same in both intervention and control groups.
3. Control group participants received placebo. We excluded trials comparing other active interventions.
4. No limit on the duration of treatment or follow-up.

Types of outcome measures

Primary outcomes

The primary outcome was acute respiratory tract infection (ARTI) frequency in children during the study period.

The diagnostic criteria for ARTI were in accordance with the Chinese Paediatrics Antibiotics Application Guideline of Acute Respiratory Tract Infection (CPSCMA 1999). We accepted a broad definition of ARTI, using different specific diagnoses, such as the common cold, influenza, sinusitis, tonsillitis, laryngitis, pharyngitis, bronchitis and pneumonia. ARTI could be either clinically confirmed or self-reported by parents in studies.

Secondary outcomes

1. Fever clearance time. This refers to the time from commencing treatment until body temperature returns to normal; self-reported by parents or reported by clinicians based on formal thermometer readings. We did not include causes of fever other than ARTI in the fever clearance time.
2. Respiratory symptom clearance time. This refers to the time from commencing treatment until respiratory symptoms resolve, such as cough and sputum reported by parents or clinicians. We planned to evaluate clearance time for each respiratory symptom.
3. Immune system indicator changes referred to changes in:
 - a. serum immunoglobulins such as IgG, IgA, or IgM; or
 - b. peripheral blood counts; or
 - c. percentage of immunocompetent cells such as haematopoietic progenitor cell, or antigen three T lymphocytes.
4. Adverse events. We planned to report all adverse events during medication administration and frequency of severe adverse events during the study period, including hospitalisations and deaths, and additional medications used in both groups.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 12 2015) (Appendix 1), MEDLINE (Ovid) (1946 to 31 December 2015) (Appendix 2), Embase (Elsevier) (Appendix 3)

(1974 to 31 December 2015), AMED (Ovid) (1985 to 31 December 2015) ([Appendix 4](#)), Chinese National Knowledge Infrastructure (CNKI) (1979 to 31 December 2015) ([Appendix 5](#)) and Chinese Scientific Journals full text database (CQVIP) (1989 to 31 December 2015) ([Appendix 6](#)), China Biology Medicine disc (CBM 1976 to 31 December 2015) ([Appendix 7](#)) and Wanfang Data Knowledge Service Platform (WanFang) (1998 to 31 December 2015) ([Appendix 8](#)).

We applied the strategy described in [Appendix 2](#) to search MEDLINE. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials ([Lefebvre 2011](#)). We adapted the search strategy to search the other databases. We did not impose language, date or publication limits.

Searching other resources

We searched the trials registries: Current Controlled Trials (www.controlled-trials.com), National Research Register (www.nihr.ac.uk), Chinese Clinical Trial Register (www.chictr.org), World Health Organization (WHO) International Clinical Trials

Registry Platform (ICTRP) (WHO ICTRP) (www.who.int/ictip/en), and ClinicalTrials.gov for completed and ongoing trials (www.clinicaltrials.gov). We planned to search the references of included studies. We attempted to identify the grey literature by searching reviews, conference proceedings and academic degree dissertations. Our search identified relevant studies published up to 31 December 2015.

Data collection and analysis

Selection of studies

Two review authors (Zhang L, Liu ZZ) scanned all titles and abstracts found in the searches. We retrieved potentially eligible studies as full-text articles and the same review authors independently assessed eligibility for inclusion. We resolved disagreements by reaching consensus after rechecking source papers and following discussion with a third review author (Liu XS). We recorded the selection process in sufficient detail to complete a PRISMA flow diagram ([Figure 1](#); [Moher 2009](#)), and [Characteristics of excluded studies](#) table.

Figure 1. Study flow diagram

Figure 1. (Continued)

Data extraction and management

We designed a data extraction form based on the checklist of items for data collection in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and as proposed by Cochrane Acute Respiratory Infections. We included information on source, eligibility, study methods, participants, intervention details, outcomes and results. All review authors reviewed the form, which was piloted using a sample of studies, and revised to produce the final version. Two review authors independently extracted data from the included trials. When more than one publication of a study existed, we planned to group reports together and to only use the publication with the most complete data in analyses. We planned to contact trial authors for study details and additional information for incomplete results in the available reports, if needed. We resolved disagreements by discussion, and when necessary, by consulting a third review author.

Assessment of risk of bias in included studies

We planned that two review authors would independently assess risk of bias of each included trial using the Cochrane 'Risk of bias' tool (Higgins 2011). Risk of bias tool domains are:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting; and
7. other sources of bias.

We planned to assign a quality rating for each domain for all included studies as high, low or unclear risk of bias.

Measures of treatment effect

We were to analyse data using Review Manager 5 (RevMan 2014). We planned to use mean difference (MD) or standardised mean difference (SMD) for continuous data, and risk ratio (RR) or odds ratio (OR) to analyse dichotomous data, both with 95% confidence intervals (CIs).

Unit of analysis issues

The individual participant was to be the unit of analysis. If the unit of analysis was not the same as the unit of randomisation, we were to adjust the outcomes for clustering based on the intra-cluster correlation as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For cross-over trials, we were only to include data from the first period. For multiple treatment groups, we were to combine all relevant

experimental intervention groups of the study into a single test group and combine all relevant control intervention groups into a single control group. We were to subject different units of analysis to a sensitivity analysis.

Dealing with missing data

We planned to obtain additional information as required by contacting study authors and to include information obtained in the review. We were to investigate attrition rates. Analyses were to be based on an intention-to-treat approach. We were to impute missing data. For missing dichotomous outcomes, we were to assume that they were ineffective in both treatment and control groups. For missing continuous outcomes, we were to try to obtain participant data by contacting authors and to impute missing data using the last observation carried forward approach (Higgins 2011). If we failed to obtain additional data, we were to perform an available-case analysis.

Assessment of heterogeneity

We planned to assess heterogeneity among trials in two steps. First, we were to assess face value heterogeneity by comparing trial populations, settings and methods. Secondly, we were to assess statistical heterogeneity using a Chi² test and the I² statistic (Higgins 2003). An I² statistic value of 25%, 50% and 75% refers to low, medium and high levels of heterogeneity, respectively. If heterogeneity were to be present, we would have examined the methodological and clinical characteristics of the included trials to explore the possible causes. We were to then conduct subgroup analyses and summarise our findings. If we had failed to identify the possible causes of heterogeneity, we were not to perform a meta-analysis. Instead, we were to use a qualitative approach to present the results.

Assessment of reporting biases

We planned to construct funnel plots if more than 10 studies were included to assess risk of publication bias. Because factors other than publication bias (such as study quality) might lead to an asymmetrical funnel plot, we were to perform Egger's test using STATA 11.0 software (StataCorp, USA) (Stata 2009), to detect funnel plot asymmetry.

Data synthesis

We planned to use a random-effects model to synthesise all data, regardless of heterogeneity among the studies. We planned to test for publication bias by constructing a funnel plot or other corrective analytical methods, depending on numbers of included studies.

GRADE and 'Summary of findings' table

We planned to create a 'Summary of findings' table using the following outcomes: ARTI frequency, fever clearance time, respiratory symptom clearance time, effectiveness rate and adverse events. We were to use the GRADE approach to rate the quality of the body of evidence based on five considerations: study limitations, consistency of effect, imprecision, indirectness and publication bias (Atkins 2004). We planned to use methods and recommendations introduced in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and the GRADE Handbook (www.guidelinedevelopment.org/handbook), using GRADEpro GDT software (GRADEpro GDT 2014). We planned to justify all decisions to downgrade or upgrade the quality of studies in footnotes, and to make comments to aid readers' understanding of the review, where necessary. We were to use Review Manager 5 for all calculations (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses based on interventions and treatment duration. Clinical heterogeneity among interventions could be related to the different doses and types of *Astragalus* preparations, such as decoction of dried *Astragalus*, powder capsule of dried *Astragalus*, capsule of *Astragalus* extracts, etc. If the onset of clinical effect and how long the effect would last were still unclear, we were to perform a subgroup analysis by stratifying by treatment duration and time of follow-up to investigate the appropriate duration of treatment.

Sensitivity analysis

We planned to perform a sensitivity analysis by stratifying studies at low, high and unclear risk of bias to explore the impact of risk of bias on the pooled estimate, and to investigate potential methodological heterogeneity. We were also to perform a sensitivity analysis with the available data to assess the impact of imputation. Analyses were not possible because no studies were found to be eligible for inclusion.

RESULTS

Description of studies

Results of the search

Searches identified a total of 6080 records: 3352 from English language databases, 2724 from Chinese databases, and four from other sources (Figure 1). After removing 1972 duplicate records, we assessed the remaining 4108, and excluded 3988 records based on titles and abstracts. We retrieved 120 full-text records and assessed them for inclusion.

Included studies

We did not identify any studies that met our inclusion criteria for this review.

Excluded studies

We excluded 120 studies, of these, 21 studies were not RCTs. We excluded a further 55 records because: participants were aged over 14 years ($n = 16$); no definition was included for recurrent or frequent episodes ($n = 25$); *Astragalus* preparation was not an intervention ($n = 1$); *Astragalus* preparation was in the formula,

but not a sole agent ($n = 3$); *Astragalus* preparation was not oral ($n = 6$); and *Astragalus* was used for treatment rather than ARTI prevention ($n = 4$). We excluded 44 records because the control was not a placebo, although other inclusion criteria were fulfilled.

We identified no ongoing studies.

Risk of bias in included studies

We were unable to conduct a 'Risk of bias' assessment because no studies were identified that met our inclusion criteria.

Effects of interventions

We did not identify any studies that met our inclusion criteria for this review.

DISCUSSION

Frequent acute respiratory tract infection (ARTI) episodes are common during childhood. Caring for children with ARTIs consumes considerable medical, parental and carer resources. In China, *Astragalus* (Huang qi) has traditionally been used to prevent ARTI. Although *Astragalus* is widely used and widely available in China, its effectiveness and safety have not been evaluated systematically in the context of ARTI prevention.

We aimed to assess the effectiveness and safety of oral *Astragalus* for preventing frequent ARTI episodes among children in community settings. However, we did not identify any studies that met our inclusion criteria. We found a gap in the evidence: well-designed and well-conducted randomised controlled trials (RCTs) investigating oral *Astragalus* to prevent frequent ARTI in children are needed to inform assessment of safety and efficacy.

A limitation of this review is that definitions of ARTI and episode frequency were not well defined. We did not find a definition for 'acute', nor whether there were differences in how episodes of upper and lower airway infections were counted, nor length of intervals between episodes. This is problematic because it can result in over- or underestimation of numbers of ARTI episodes reported.

Another limitation was that ARTI frequency in children was the only primary outcome; ARTI severity and duration are also very important to evaluate the effect of prevention. Instruments such as the Wisconsin Upper Respiratory Symptom Survey for Kids (WURSS-K) and the Canadian Acute Respiratory Infection and Flu Scale (CARFIS) have been developed to enable evaluation of severity and duration of RTIs among children (Fischer 2014; Jacobs 2000; Shepperd 2004; www.fammed.wisc.edu/wurss). WURSS-K is a self-report quality of life instrument for children, designed to assess the negative impact of acute URTI. WURSS-K is completed by children and focuses on the impact of quality of life; CARFIS is used by parents and focuses on ARTI severity. Both instruments could be used in future studies looking at the preventive effect of *Astragalus* for children with frequent episodes of ARTI.

We did not capture the exact ingredients of the intervention in the inclusion criteria. As a natural product, the method of plant extraction and whether the product is standardised will determine the proportion of constituents and dose, thus influencing effectiveness and safety of oral *Astragalus* preparations. The aspects of standardisation of oral *Astragalus* preparation should be

considered, such as which part of the plant was used, species, age, size, growing conditions, medicinal preparations/extract methods, proportion of constituents, and storage methods of *Astragalus* (Natural Medicines 2016), all of which have implication for future research.

Summary of main results

We did not identify any RCTs that investigated the effectiveness and safety of oral *Astragalus* compared with placebo to prevent frequent episodes of ARTIs in children.

Overall completeness and applicability of evidence

We did not identify any RCTs for inclusion.

Quality of the evidence

We did not identify any RCTs for inclusion.

Potential biases in the review process

We found no studies that met our inclusion criteria; our search strategies were comprehensive, and it is unlikely that we missed potentially eligible studies. We included two additional Chinese language databases (CBM and Wanfang) than planned in the protocol, to extend our search and capture all potential studies.

We planned to include only placebo-controlled studies and ARTI was to be clinically confirmed or self-reported by patients. Since patient-reported occurrence of ARTI is subjective, placebo was nominated as the only control that would avoid expectation and measurement bias. We did not find any studies that were placebo-controlled, and surmised that difficulties in obtaining ethics approval, especially in trials for children, limited this objective. Obtaining informed consent could be challenging because of reluctance by parents and carers to consent to children's participation in the knowledge that they may be allocated to the placebo arm. Of the 44 studies that fulfilled all inclusion criteria, except being placebo-controlled, most were add-on design studies (Huang qi + concurrent treatment versus concurrent treatment). Further evaluation of the add-on effect might be possible by reviewing these studies.

Agreements and disagreements with other studies or reviews

We found no studies or systematic reviews that investigated the effectiveness and safety of oral *Astragalus* in preventing frequent ARTIs in children. Current evidence is diverse in study design but all support oral *Astragalus* in preventing ARTIs in children, such as the 44 non-placebo-controlled RCTs excluded from this review, and a mini systematic review embedded in a case report of Huang

qi (*Astragalus*) granules in upper respiratory tract infection (URTI) prevention in children with nephrotic syndrome (Zou 2013).

AUTHORS' CONCLUSIONS

Implications for practice

Although oral *Astragalus* (Huang qi) has been used to prevent acute respiratory tract infection (ARTI) for many years, no placebo-controlled randomised controlled trial (RCT) evidence is available to help guide practice, family decisions about care, or healthcare policy in relation to oral *Astragalus* for preventing frequent ARTI episodes among children in community settings.

Implications for research

Large, well-designed RCTs investigating the safety and efficacy of oral *Astragalus* to prevent frequent ARTIs in children are needed. In future studies, add-on placebo designs (Huang qi + concurrent treatment versus placebo + concurrent treatment) may help to prevent children not receiving any treatment. Consideration should be taken to include:

1. the use of WRUSS-K and CARFIS instruments to evaluate quality of life and disease severity, rather than ARTI frequency;
2. a clear definition of 'acute' in relation to respiratory tract infection, and stating the interval between respiratory tract infection episodes used to define separate episodes;
3. standardising ingredients and dosage of oral *Astragalus* used in children and ensuring the placebo is adequately masked to replicate the smell and taste of oral *Astragalus*;
4. systemic markers of immune function to see the potential mechanism; and
5. if a placebo is not applicable, pragmatic research in real world practice to evaluate the preventive and safety effects of oral *Astragalus* in children with frequent ARTIs.

ACKNOWLEDGEMENTS

We thank Cochrane Acute Respiratory Infections for their assistance with this Cochrane Review. The authors would also like to thank Suzanne Cunliffe, Lily Lai, George Lewith, David King, Viviana Rodriguez and Susan Smith for their comments on the protocol; and Ann Fonfa, Eleana Villanueva, George Lewith, Mio Hu, Treasure McGuire, Viviana Rodriguez and Susan Smith for their comments on the review. We would also like to thank Oliver Dyar for checking grammar and commenting on this review. We acknowledge Jiasheng Huang and Jiawei He for their management and editing of text and data in this review. We thank Liz Dooley, Kerry Dwan, Ann Jones and other editors for their editing work on this review.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bai 2005	Not placebo-controlled
Chen 1996	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; participants were aged over 14 years; intervention aimed for treatment, not prevention
Chen 2001	RTIs investigated, but not defined as recurrent or frequent episodes; not oral <i>Astragalus</i> preparation
Chen 2003	Not placebo-controlled
Chen 2008a	RTIs investigated, but not defined as recurrent or frequent episodes; non-RCT
Chen 2008b	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Chen 2009	Not placebo-controlled
Chen 2010	Not oral <i>Astragalus</i> preparation
Cui 2010	RTIs investigated, but not defined as recurrent or frequent episodes; not oral <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Deng 2000	Not placebo-controlled
Deng 2004	Not placebo-controlled

Wu 2007

Wu T, Zhang J, Qiu Y, Xie L, Liu GJ. Chinese medicinal herbs for the common cold. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: [10.1002/14651858.CD004782.pub2](https://doi.org/10.1002/14651858.CD004782.pub2)]

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Study	Reason for exclusion
Du 1992	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Feng 2001	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; participants were aged over 14 years; intervention aimed for treatment, not prevention
Feng 2009	RTIs investigated, but not defined as recurrent or frequent episodes
Gao 1993	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; participants were aged over 14 years; intervention aimed for treatment, not prevention
Gao 2007	Not placebo-controlled
Guan 2011	Not placebo-controlled
Guo 2008	Non-RCT
Han 2000	Not placebo-controlled
Han 2011	Not placebo-controlled
He 2014	Non-RCT
Hu 1984	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Huang 2000	Not placebo-controlled
Huang 2004a	No data; Only for treatment not for prevention
Huang 2004b	Not placebo-controlled
Huang 2012a	Not oral <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Huo 1994	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Ikeda 1988	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; non-RCT; intervention aimed for treatment, not prevention
Ji 1996	RTIs investigated, but not defined as recurrent or frequent episodes; <i>Astragalus</i> preparation not administered as sole agent; participants were aged over 14 years; intervention aimed for treatment, not prevention
Jin 1997	Not oral <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Jin 2009	<i>Astragalus</i> preparation not administered as sole agent; intervention aimed for treatment, not prevention
Jin 2013	Not placebo-controlled
Kang 1992	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Ke 2005	Non-RCT

Study	Reason for exclusion
Li 1989	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; participants were aged over 14 years; intervention aimed for treatment, not prevention
Li 1994a	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; non-RCT; intervention aimed for treatment, not prevention
Li 1994b	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Li 1999	RTIs investigated, but not defined as recurrent or frequent episodes; intervention aimed for treatment, not prevention
Li 2001	RTIs investigated, but not defined as recurrent or frequent episodes; <i>Astragalus</i> preparation not administered as sole agent; participants were aged over 14 years; intervention aimed for treatment, not prevention
Li 2002	Not placebo-controlled
Li 2004	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Li 2008	Not placebo-controlled
Li 2013	Not placebo-controlled
Li 2015	Not oral <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Lin 2001	Not placebo-controlled
Lin 2003	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Lin 2012	Not placebo-controlled
Liu 1992	Non-RCT; intervention aimed for treatment, not prevention
Liu 2002	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Liu 2003	Not placebo-controlled
Liu 2004a	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; participants were aged over 14 years; intervention aimed for treatment, not prevention
Liu 2004b	RTIs investigated, but not defined as recurrent or frequent episodes; not oral <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Liu 2004c	Not placebo-controlled
Liu 2010	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Liu 2011	Not placebo-controlled
Liu 2014	RTIs investigated, but not defined as recurrent or frequent episodes; not oral <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention

Study	Reason for exclusion
Lu 2006	RTIs investigated, but not defined as recurrent or frequent episodes; non-RCT
Lu 2009	Not placebo-controlled
Lu 2012	RTIs investigated, but not defined as recurrent or frequent episodes; <i>Astragalus</i> preparation not administered as sole agent; participants were aged over 14 years; intervention aimed for treatment, not prevention
Lu 2013	Not placebo-controlled
Luan 2001	Not placebo-controlled
Luo 1994	RTIs investigated, but not defined as recurrent or frequent episodes; <i>Astragalus</i> preparation not administered as sole agent; participants were aged over 14 years
Luo 2013	Not placebo-controlled
Nie 2009a	Not oral <i>Astragalus</i> preparation
Peng 1991	RTIs investigated, but not defined as recurrent or frequent episodes; <i>Astragalus</i> preparation not administered as sole agent; participants were aged over 14 years; intervention aimed for treatment, not prevention
Peng 2006	Intervention aimed for treatment, not prevention
Peng 2012	RTIs investigated, but not defined as recurrent or frequent episodes; intervention aimed for treatment, not prevention
Qi 2000	RTIs investigated, but not defined as recurrent or frequent episodes; <i>Astragalus</i> preparation not administered as sole agent; participants were aged over 14 years; intervention aimed for treatment, not prevention
Qiu 2004	Non-RCT
Ruan 2013	Not placebo-controlled
Shen 1988	Non-RCT; intervention aimed for treatment, not prevention
Sheng 2010	Not placebo-controlled
Shi 2006	RTIs investigated, but not defined as recurrent or frequent episodes; participants were aged over 14 years
Song 2008	Not placebo-controlled
Su 1988	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Su 1994	RTIs investigated, but not defined as recurrent or frequent episodes; <i>Astragalus</i> preparation not administered as sole agent; intervention aimed for treatment, not prevention
Wang 1997	Non-RCT; <i>Astragalus</i> preparation not administered as sole agent
Wang 2001	Not placebo-controlled
Wang 2008a	RTIs investigated, but not defined as recurrent or frequent episodes; non-RCT

Study	Reason for exclusion
Wang 2008b	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Wang 2009	Not placebo-controlled
Wang 2010	Only for treatment not for prevention
Wang 2013	Not placebo-controlled
Wang 2014	Not placebo-controlled
Wang 2015	Not placebo-controlled
Wei 2000	Not oral <i>Astragalus</i> preparation
Wu 1996	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; participants were aged over 14 years; intervention aimed for treatment, not prevention
Wu 2003	Non-RCT
Wu 2011	RTIs investigated, but not defined as recurrent or frequent episodes; non-RCT; intervention aimed for treatment, not prevention
Xia 2007	RTIs investigated, but not defined as recurrent or frequent episodes; intervention aimed for treatment, not prevention
Xiao 1988	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Xiao 2014	Not placebo-controlled
Xie 2015	Intervention aimed for treatment, not prevention
Xu 1994	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; participants were aged over 14 years; intervention aimed for treatment, not prevention
Xu 1997	<i>Astragalus</i> preparation not administered as sole agent
Xu 2004	Non-RCT; not oral <i>Astragalus</i> preparation
Yang 1992	RTIs investigated, but not defined as recurrent or frequent episodes; <i>Astragalus</i> preparation not administered as sole agent; participants were aged over 14 years; intervention aimed for treatment, not prevention
Yang 1998	Not placebo-controlled
Yang 2001	Not placebo-controlled
Yang 2008	Non-RCT
Yu 2005	Non-RCT
Zeng 2009	RTIs investigated, but not defined as recurrent or frequent episodes

Study	Reason for exclusion
Zhang 1995	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Zhang 1999	Not placebo-controlled
Zhang 2000	Intervention aimed for treatment, not prevention
Zhang 2012	Not placebo-controlled
Zhang 2013	Not placebo-controlled
Zhao 2000a	RTIs investigated, but not defined as recurrent or frequent episodes; not <i>Astragalus</i> preparation; participants were aged over 14 years; intervention aimed for treatment, not prevention
Zhao 2000b	Non-RCT
Zhao 2003	Not placebo-controlled
Zhao 2007	Not oral <i>Astragalus</i> preparation
Zheng 2013	RTIs investigated, but not defined as recurrent or frequent episodes; not oral <i>Astragalus</i> preparation; intervention aimed for treatment, not prevention
Zhong 2012	Not placebo-controlled
Zhou 2005	RTIs investigated, but not defined as recurrent or frequent episodes; non-RCT
Zhou 2009a	Not placebo-controlled
Zhou 2009b	Non-RCT
Zhou 2012	Not placebo-controlled
Zhu 2014a	<i>Astragalus</i> preparation not administered as sole agent
Zhu 2014b	RTIs investigated, but not defined as recurrent or frequent episodes; <i>Astragalus</i> preparation not administered as sole agent; non-RCT
Zou 2000	Not placebo-controlled

ADDITIONAL TABLES

Table 1. Definition of frequent episodes of respiratory tract infection

Age (years)	Recurrent URTI (episodes per year)	Recurrent LRTI (episodes per year)	
		Recurrent tracheitis or bronchitis	Recurrent pneumonia
Birth to 2 years of age	7	3	2
2 to 5 years of age (> 2 years and < 5 years)	6	2	2

Table 1. Definition of frequent episodes of respiratory tract infection (Continued)

5 to 14 years of age (> 5 years and < 14 years)	5	2	2
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Abbreviations: LRTI - lower respiratory tract infection; URTI - upper respiratory tract infection

APPENDICES

Appendix 1. CENTRAL search strategy

1 MeSH descriptor: [*Astragalus* Plant] explode all trees

2 Astraga*

3 MeSH descriptor: [*Astragalus membranaceus*] explode all trees

4 Huang Qi

5 Huangqi

6 Milkvetch

7 #1 OR #2 OR #3 OR #4 OR #5 OR #6

8 MeSH descriptor: [Drugs, Chinese Herbal] explode all trees

9 MeSH descriptor: [Medicine, East Asian Traditional] explode all trees

10 MeSH descriptor: [Phytotherapy] explode all trees

11 MeSH descriptor: [Herbal Medicine] explode all trees

12 MeSH descriptor: [Plants, Medicinal] explode all trees

13 MeSH descriptor: [Plant Preparations] explode all trees

14 (Chinese) AND ((Prescription*) OR (Preparation*) OR (extract*) OR (herb*) OR (medicin*) OR (drug*) OR (plant*) OR (botanical*))

15 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

16 MeSH descriptor: [Respiratory Tract Infections] explode all trees

17 (acute OR upper OR lower) AND ((respiratory infection*) OR (respiratory tract infection*))

18 (pharyngit*) OR (tracheit*) OR (bronchit*) OR (pneumon*)

19 (common cold*) OR (coryza) OR (influenza*) OR (flu) OR (otitis media*) OR (sinusit*) OR (tonsillit*) OR (laryngit*) OR (pharyngit*) OR (bronchit*) OR (pneumon*) OR (sore throat*) OR (sneez*) OR (cough*) OR ((nasal or nose) AND (congest* or discharg*))

20 #16 OR #17 OR #18 OR #19

21 #15 and #20

22 #7 OR #21

Appendix 2. MEDLINE (Ovid) search strategy

1 exp *Astragalus* Plant/

2 Astragal*.mp.

3 "A. membranaceus".mp.

4 "huang qi".mp.

5 huangqi.mp.

6 vetch.mp.

7 or/1-6

8 Drugs, Chinese Herbal/

9 exp Medicine, East Asian Traditional/

10 Phytotherapy/

11 Herbal Medicine/

12 Plants, Medicinal/

13 plant preparations/ or plant extracts/

14 (chinese adj5 (herb* or medicin* or drug* or plant* or botanical*)).mp.

15 or/8-14

16 exp Respiratory Tract Infections/

17 ((acute or upper or lower) adj2 (respiratory infection* or respiratory tract infection*)).mp.

18 (pharyngit* or tracheit* or bronchit* or pneumon*).mp.

19 (common cold* or coryza or influenza* or flu or otitis media* or sinusit* or tonsillit* or laryngit* or pharyngit* or bronchit* or pneumon* or sore throat* or sneez* or cough* or ((nasal or nose) adj2 (congest* or discharg*))).mp.

20 or/16-19

21 15 and 20

22 7 or 21

23 randomized controlled trial.pt.

24 controlled clinical trial.pt.

25 randomized.ab.

26 placebo.ab.

27 clinical trials as topic.sh.

28 randomly.ab.

29 trial.ti.

30 or/23-29

31 exp animals/ not humans.sh.

32 30 not 31

33 22 and 32

Appendix 3. Embase (Elsevier) search strategy

1 *Astragalus* (plant)'/exp

2 Astragal*

3 "A. membranaceus"

4 "huang qi"

5 "huangqi"

6 vetch

7 #1 OR #2 OR #3 OR #4 OR #5 OR #6

8 Chinese herb'/exp

9 oriental medicine'/exp

10 phytotherapy'/exp

11 'herbal medicine'/exp

12 medicinal plant'/exp

13 ('plant medicinal product'/exp) or ('plant extract'/exp)

14 chinese NEXT/5 (herb* or medicin* or drug* or plant* or botanical*)

15 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

16 respiratory tract infection'/exp

17 respiratory AND infection* OR (respiratory AND tract AND infection*)

18 pharyngit* or tracheit* or bronchit* or pneumon*

19 common cold* or coryza or influenza* or flu or otitis media* or sinusit* or tonsillit* or laryngit* or pharyngit* or bronchit* or pneumon* or sore throat* or sneez* or cough* or ((nasal or nose) NEXT/2 (congest* or discharg*))

20 #16 AND #17 AND #18 AND #19

21 #15 and #20

22 #7 or #21

23 [randomized controlled trial]/lim

24 [controlled clinical trial]/lim

25 randomized:ab

26 placebo:ab

27 clinical trial (topic)'/exp

28 randomly:ab

29 trial:ti

30 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29

31 animal'/exp not 'human'/exp

32 #30 not #31

33 #22 and #32

Appendix 4. AMED (Ovid) search strategy

1 exp *Astragalus* Plant/

2 Astragal*.mp.

3 "A. membranaceus".mp.

4 "huang qi".mp.

5 huangqi.mp.

6 vetch.mp.

7 or/1-6

8 Drugs, Chinese Herbal/

9 exp Medicine, East Asian Traditional/

10 Phytotherapy/

11 Herbal Medicine/

12 Plants, Medicinal/

13 plant preparations/ or plant extracts/

14 (chinese adj5 (herb* or medicin* or drug* or plant* or botanical*)).mp.

15 or/8-14

16 exp Respiratory Tract Infections/

17 ((acute or upper or lower) adj2 (respiratory infection* or respiratory tract infection*)).mp.

18 (pharyngit* or tracheit* or bronchit* or pneumon*).mp.

19 (common cold* or coryza or influenza* or flu or otitis media* or sinusit* or tonsillit* or laryngit* or pharyngit* or bronchit* or pneumon* or sore throat* or sneez* or cough* or ((nasal or nose) adj2 (congest* or discharg*))).mp.

20 or/16-19

21 15 and 20

22 7 or 21

23 randomized controlled trial.pt.

24 controlled clinical trial.pt.

25 randomized.ab.

26 placebo.ab.

27 clinical trials as topic.sh.

28 randomly.ab.

29 trial.ti.

30 or/23-29

31 exp animals/ not humans.sh.

32 30 not 31

33 22 and 32

Appendix 5. CNKI search strategy

SU= ("呼吸道感染"+"感冒"+"流感"+"喉炎"+"咽炎"+"肺炎"+"肺部感染"+"鼻炎"+"鼻窦炎"+"扁桃体炎"+"气管炎"+"结核"+"百日咳") AND SU= ("黄芪"+"北芪"+"黄耆"+"北耆") AND SU= ("临床观察"+"临床评估"+"临床试验"+"临床效果"+"临床研究"+"疗效"+"评价研究"+"前瞻性"+"随访"+"对比研究"+"多中心"+"随机"+"对照"+"病例报告"+"病例研究"+"病例分析"+"病例报道")

Appendix 6. CQVIP search strategy

题名或关键词

M(题名或关键词)=(呼吸道感染+感冒+流感+喉炎+咽炎+肺炎+肺部感染+鼻炎+鼻窦炎+扁桃体炎+气管炎+结核+百日咳)*(黄芪+北芪+黄耆+北耆)*(临床观察+临床评估+临床试验+临床效果+临床研究+疗效+评价研究+前瞻性+随访+对比研究+多中心+随机+对照+病例报告+病例研究+病例分析+病例报道)

文摘

R(文摘)=(呼吸道感染+感冒+流感+喉炎+咽炎+肺炎+肺部感染+鼻炎+鼻窦炎+扁桃体炎+气管炎+结核+百日咳)*(黄芪+北芪+黄耆+北耆)*(临床观察+临床评估+临床试验+临床效果+临床研究+疗效+评价研究+前瞻性+随访+对比研究+多中心+随机+对照+病例报告+病例研究+病例分析+病例报道)

Appendix 7. CBM search strategy

#1:((((("呼吸道感染"[常用字段:智能]) OR "感冒"[常用字段:智能]) OR "流感"[常用字段:智能]) OR "喉炎"[常用字段:智能]) OR "咽炎"[常用字段:智能]) OR "肺炎"[常用字段:智能]) OR "肺部感染"[常用字段:智能])

#2:((((("鼻炎"[常用字段:智能]) OR "鼻窦炎"[常用字段:智能]) OR "扁桃体炎"[常用字段:智能]) OR "气管炎"[常用字段:智能]) OR "结核"[常用字段:智能]) OR "百日咳"[常用字段:智能])

#3: (#2) OR (#1)

#4: (((("黄芪"[常用字段:智能]) OR "北芪"[常用字段:智能]) OR "黄耆"[常用字段:智能]) OR "北耆"[常用字段:智能])

#5: (((((((("临床观察"[常用字段:智能]) OR "临床评估"[常用字段:智能]) OR "临床试验"[常用字段:智能]) OR "临床效果"[常用字段:智能]) OR "临床研究"[常用字段:智能]) OR "疗效"[常用字段:智能]) OR "评价研究"[常用字段:智能]) OR "前瞻性"[常用字段:智能])

#6: (((((((("随访"[常用字段:智能]) OR "对比研究"[常用字段:智能]) OR "多中心"[常用字段:智能]) OR "随机"[常用字段:智能]) OR "对照"[常用字段:智能]) OR "病例报告"[常用字段:智能]) OR "病例研究"[常用字段:智能]) OR "病例分析"[常用字段:智能]) OR "病例报道"[常用字段:智能])

#7: (#6) OR (#5)

#8: (#7) AND (#4) AND (#3)

Appendix 8. Wanfang search strategy

主题词

主题: ("呼吸道感染"+"感冒"+"流感"+"喉炎"+"咽炎"+"肺炎"+"肺部感染"+"鼻炎"+"鼻窦炎"+"扁桃体炎"+"气管炎"+"结核"+"百日咳") AND 主题: ("黄芪"+"北芪"+"黄耆"+"北耆") AND 主题: ("临床观察"+"临床评估"+"临床试验"+"临床效果"+"临床研究"+"疗效"+"评价研究"+"前瞻性"+"随访"+"对比研究"+"多中心"+"随机"+"对照"+"病例报告"+"病例研究"+"病例分析"+"病例报道")

CONTRIBUTIONS OF AUTHORS

Guobin Su and Xusheng Liu drafted the review.

Xiankun Chen and Zhuangzhu Liu developed and ran the search strategy.

Lihong Yang and La Zhang independently extracted data and obtained copies of studies.

Xindong Qin and Jueyao Liang entered data into Review Manager 5.

Zhuangzhu Liu and Zehuai Wen assessed studies for inclusion and planned to assess risk of bias.

Xinfeng Guo was the third review author who planned to select which studies to include when disagreements existed.

Cecilia Stålsby Lundborg contributed to the development of data analysis strategies and acted as a general adviser.

Xusheng Liu acted as guarantor for the review and planned to perform data analysis.

All authors provided comments on this review and approved the final version.

DECLARATIONS OF INTEREST

Guobin Su: none known.

Xiankun Chen: none known.

Zhuangzhu Liu: none known.

Lihong Yang: none known.

La Zhang: none known.

Cecilia Stålsby Lundborg: none known.

Zehuai Wen: none known.

Xinfeng Guo: none known.

Xindong Qin: none known.

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Xusheng Liu: none known.

SOURCES OF SUPPORT

Internal sources

- Guangdong Provincial Hospital of Chinese Medicine, China.

This review is supported by a research grant from a project between the Guangdong Provincial Hospital of Chinese Medicine in China and the Department of Public Health Sciences, Karolinska Institutet in Sweden.

External sources

- Provincial Administration of Traditional Chinese Medicine, Guangdong Province, China.

This review is supported by a research fund for developing Guangdong Province as a competitive province of traditional Chinese medicine (NO. 20151245) by the Provincial Administration of Traditional Chinese Medicine, Guangdong Province, China.

- China Scholarship Council, China.

Guobin Su is supported by China Scholarship Council. (NO. 201508440214)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added two Chinese language databases (CBM and Wanfang) to extend our search to capture all potential studies. Planned analyses could not be conducted because no studies met our inclusion criteria.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Oral; Drugs, Chinese Herbal [*therapeutic use]; Respiratory Tract Infections [*prevention & control]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant