

Chinese medicinal herbs for influenza (Review)

Chen XY, Wu T, Liu GJ, Wang Q, Zheng J, Wei J, Ni J, Zhou L, Duan X, Qiao J



**THE COCHRANE
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 2

<http://www.thecochranelibrary.com>



Chinese medicinal herbs for influenza (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	5
METHODS	5
RESULTS	8
DISCUSSION	15
AUTHORS' CONCLUSIONS	17
ACKNOWLEDGEMENTS	17
REFERENCES	18
CHARACTERISTICS OF STUDIES	20
DATA AND ANALYSES	25
Analysis 1.1. Comparison 1 Day 2 recovery rate, Outcome 1 Herbal medicine versus antiviral drugs.	26
Analysis 2.1. Comparison 2 Day 3 recovery rate, Outcome 1 Herbal medicine versus antiviral drugs.	27
Analysis 3.1. Comparison 3 Day 3 marked improvement, Outcome 1 Herbal medicine versus antiviral drugs.	27
Analysis 4.1. Comparison 4 Day 3 partial improvement, Outcome 1 Herbal medicine versus antiviral drugs.	28
Analysis 5.1. Comparison 5 Day 3 no improvement rate, Outcome 1 Herbal medicine versus antiviral drugs.	28
Analysis 6.1. Comparison 6 Influenza incidence, Outcome 1 Herbal medicine versus antiviral drugs.	29
Analysis 7.1. Comparison 7 Adverse reaction, Outcome 1 Adverse reaction in the gastrointestinal tract.	29
WHAT'S NEW	29
HISTORY	30
CONTRIBUTIONS OF AUTHORS	30
DECLARATIONS OF INTEREST	30
SOURCES OF SUPPORT	31
INDEX TERMS	31

[Intervention Review]

Chinese medicinal herbs for influenza

Xiao Y Chen¹, Taixiang Wu², Guan J Liu², Qin Wang³, Jie Zheng⁴, Jiafu Wei⁴, Juan Ni⁴, Likun Zhou⁴, Xin Duan⁵, Jieqi Qiao⁴

¹Department of Neurology, The General Hospital of the People's Liberation Army (PLAGH) (also Hospital 301), Beijing, China.

²Chinese Cochrane Centre, Chinese EBM Centre, West China Hospital, Sichuan University, Chengdu, China. ³Endocrinology Department, West China Hospital, Sichuan University, Chengdu, China. ⁴Clinical Epidemiology, West China Hospital of Sichuan University, Chengdu, China. ⁵Department of Orthopaedic Surgery, West China Hospital of Sichuan University, Chengdu, China

Contact address: Xiao Y Chen, Department of Neurology, The General Hospital of the People's Liberation Army (PLAGH) (also Hospital 301), Fuxing Road 28, Beijing, Beijing, 100853, China. abilitywin@163.com. abilitywin@hotmail.com, abilitywin@chinaren.com.

Editorial group: Cochrane Acute Respiratory Infections Group.

Publication status and date: Edited (no change to conclusions), published in Issue 2, 2010.

Review content assessed as up-to-date: 31 December 2006.

Citation: Chen XY, Wu T, Liu GJ, Wang Q, Zheng J, Wei J, Ni J, Zhou L, Duan X, Qiao J. Chinese medicinal herbs for influenza. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD004559. DOI: 10.1002/14651858.CD004559.pub3.

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Influenza is an acute respiratory communicable disease which, during epidemics, can cause high morbidity and mortality. Traditional Chinese medicinal herbs, often administered following a particular theory, may be a potential medicine of choice.

Objectives

To assess the effect of Chinese medicinal herbs in preventing and treating influenza, and to estimate the frequency of adverse effects.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, issue 1), which includes the Cochrane Acute Respiratory Infections Review Group specialised register; MEDLINE (January 1966 to January 2007); EMBASE (January 1988 to January 2007); CBM (Chinese Biomedical Database) (January 1980 to January 2007); and the Chinese Cochrane Center's Controlled Trials Register (up to January 2007). We also searched Current Controlled Trials (www.controlled-trials.com) and the National Research Register (<http://www.update-software.com/National/>) for ongoing trials and reference lists of articles. For more information we telephoned and wrote to researchers in the field, as well as trial authors of studies evaluated in the review

Selection criteria

Randomised controlled trials (RCTs) comparing traditional Chinese medicinal herbs with placebo, no treatment, or chemical drugs normally used in preventing and treating uncomplicated influenza patients.

Data collection and analysis

Two review authors independently extracted data and assessed trial quality.

Main results

Two studies involving 1012 participants were reviewed. The methodological quality of both studies was 'poor'. Included RCTs separately compared two medicinal herbs with two different antiviral drugs, precluding any pooling of results. 'Ganmao' capsules were found to be more effective than amantadine in decreasing influenza symptoms and speeding recovery in one study, (in which adverse reactions were mentioned in the amantadine group although no data were reported). There were no significant differences between 'E Shu You' and ribavirin in treating influenza, nor in the occurrence of adverse reaction.

Chinese medicinal herbs for influenza (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

1

Authors' conclusions

The present evidence is too weak to support or reject the use of Chinese medicinal herbs for preventing and treating influenza. More RCTs with good methodological quality, larger numbers of participants and clear reporting are needed in the future. We recommend that all the clinical trials registered in the Chinese Clinical Trial Register and Chinese journals join in the Joint Statement of Establishing Chinese Clinical Trial Registration and Publishing System.

PLAIN LANGUAGE SUMMARY

Chinese medicinal herbs for patients with uncomplicated influenza

Influenza can cause high morbidity and mortality in an epidemic. Many Chinese medicinal herbs are used for this condition. This review assessed the prophylactic and therapeutic effects as well as safety of Chinese medicinal herbs as an alternative and adjunctive medicine to other commonly used drugs for uncomplicated influenza. Two studies involving 1012 participants were included in the review. The trial quality and evidence were poor and do not support or reject the use of any Chinese herbal preparations for influenza. Well-designed trials are required.

BACKGROUND

Description of the condition

Influenza is an acute respiratory illness caused by a virus from the Orthosynovitic family, of which three serotypes are known (A, B and C). Influenza causes an acute febrile illness with myalgia, headache and cough. Uncomplicated influenza generally resolves over a two to five day period. However, in a significant minority, symptoms of weakness and malaise may persist for several weeks, particularly in the elderly. Complications of influenza include otitis media, pneumonia, exacerbation of chronic respiratory disease, croup and bronchiolitis. Additionally, influenza can cause a range of non-respiratory complications including febrile convulsions, Reyes's syndrome and myocarditis (Wiselka 1994). The influenza virus is transmitted primarily via virus-laden large droplets from sneezing, coughing or talking. Transmission may also occur by direct (for example, person-to-person) or indirect (person-to fomite-to person) contact (CDC 2007).

Influenza virus types (A, B or C) are based on antigenic characteristics of the nucleoproteins and matrix protein antigens. However, the influenza virus genome is segmented and there is a high frequency for re-arrangements of the genes (Ahmed 1996; Buda 2000). A major factor in determining the severity and spread of influenza outbreaks is the level of immunity present in the population at risk. When an antigenically new influenza virus emerges in a community where few or no antibodies are present, extensive

outbreaks may occur (Claas 1998; Fleming 1999). Annual epidemics are thought to result in between three and five million cases of severe influenza, and between 250,000 and 500,000 deaths annually (WHO 2003). The outbreak in humans of an H5N1 avian influenza virus in Hong Kong in 1997 has increased awareness of our vulnerability to a global pandemic. Since late 2003 the accelerated geographical spread of influenza A (H5N1) among birds has heightened concerns. Up until early 2007, more than 250 confirmed cases of human infection with influenza A (H5N1) in 10 countries have been reported to the World Health Organization (WHO) (WHO 2007).

Description of the intervention

Annual vaccination is the primary strategy for preventing influenza. Over-the-counter (OTC) medications for controlling influenza symptoms may be recommended and antiviral medications can be prescribed. Four influenza antiviral agents (amantadine, rimantadine, zanamivir and oseltamivir*) have been approved by the US Food and Drug Administration (FDA). Amantadine and rimantadine are effective against influenza A viruses. However, high levels of drug resistance have been recorded, and the Advisory Committee on Immunization Practices (ACIP) recommends that neither amantadine nor rimantadine be used for the treatment or chemoprophylaxis against influenza A in the USA until susceptibility to these antiviral medications has been re-es-

established. Zanamivir and oseltamivir are neuraminidase inhibitors effective against both influenza A and B viruses. Oseltamivir is approved for the treatment of people aged over one year, and zanamivir for people aged over seven years. These medications should be taken within two days after the onset of symptoms and continued for five to seven days. They have been shown to lessen both the severity and duration of uncomplicated influenza (Smith 2006). Careful use of these products is encouraged because of the emergence of resistant influenza strains (HamiltonBaldwin 2000; Moscona 2005). Dosing and side effects vary depending on the drug, age, hepatic and renal functions. The major side effects tend to affect the central nervous system (CNS) and the gastrointestinal tract. Other side effects include light-headedness, nervousness, anxiety, difficulty in concentration, diarrhoea, and anorexia. Caution should be used when taking OTC agents and amantadine (HamiltonBaldwin 2000).

Traditional Chinese medicine (TCM) follows a particular theoretical and methodological pathway of assessing the cause, diagnosis and treatment. Chinese medicinal herbs, the most important component of TCM, are derived from plants and usually incorporate one or more herbs as the basic drug(s) to treat the disease. Depending upon the different symptoms or causes, the herbs are selected and mixed together, following a particular process, to form the prescription.

The different ingredients in each plant work synergistically to balance the body. This prescription rule is similar to Western medical systems. It is said that herbal remedies have fewer side effects than orthodox therapies with chemical entities. It is not that there are no toxic effects, but that plants are a natural source. Humans have co-evolved with and are adept at using herbal remedies. The preparation of a remedy from a more toxic plant often discards (unless this is specifically required) the actual toxic component and leaves the useful components (Cezanne 1997).

How the intervention might work

In TCM the aim in treating influenza is not only to cure the respiratory symptoms, but also to treat the whole body. In TCM, influenza is differentiated into two types: Wind-cold Syndrome and Wind-heat Syndrome. The main symptoms of Wind-cold type are: severe cold, slight fever, absence of sweat, headache, aching pain of extremities, stuffy nose with nasal discharge, cough with thin sputum, thin, whitish coating on the tongue, and a floating and tight pulse (Zhao 2001). The principles behind treating this type are to: relieve external symptoms with drugs which are pungent in flavour and warm in property; ventilate the lungs and expel the pathogenic cold. Herba Schizonepetae, Radix Ledebouriellae, Radix Bupleuri, Radix Platycodi, and Rhizoma Zingiberis Recens are usually the main components for a prescription for Wind-cold Syndrome. Moreover, supplementary drugs may be added when particular symptoms are present.

The main symptoms of Wind-heat type are: a high fever, slight aversion to cold, headache, sore throat with congestion, expectoration of yellowish sputum, thirst, epistaxis, reddened tongue with a thin, yellowish coating, and a floating and rapid pulse (Zhao 2001). The principles behind treating this type are to: relieve external symptoms with drugs which are pungent in flavour and cool in property and promote the dispersing function of the lungs and clear up pathogenic heat. Flos Lonicerae, Fructus Forsythiae, Radix Isatidis, Radix Puerariae, Folium Mori, Flos Chrysanthemi, Fructus Arctii, Herba Lophatheri, and Radix Platycodi are usually the main components of a prescription for Wind-heat Syndrome. Supplementary drugs are sometimes added according to certain symptoms (Deng 1998; Hou 1995; Liu 2001; Ou 1992; Xu 1998; Zhang 1991). (See Table 1).

Table 1. Medicinal herbs for influenza

Latin name	Common name	Properties, tastes	Function
Herba Schizonepetae	Schizonepeta	Pungent, slightly warm	1. Expel wind, release the symptoms. 2. Promote the formation of eruption. 3. Stop bleeding and ablate boils. 4. Restrains and kills bacteria. 5. Tranquilliser, analgesic. 6. Anti-inflammation, anti allergy
Radix Ledebouriellae	Ledebouriella root	Pungent, slightly warm	1. Expel wind and relieve the symptoms. 2. Expel wind, dampness and alleviates pain. 3. Antipyretic, antiinflammatory, analgesic. 4. Relieve spasms. 5. Stops diarrhoea

Table 1. Medicinal herbs for influenza (Continued)

Radix Bupleuri	Bupleurum root	Pungent, bitter and slightly cold	1. Reduce and disperse fever. 2. Relax constrained “gan qi” and alleviate mental depression. 3. Improve immune function. 4. Regulate the flow of “qi” to relieve pain. 5. Tranquillises the mind, stop coughing. 6. Anti-inflammatory, anti-influenza, anti-mycobacterium, tuberculosis. 7. Reduce plasma cholesterol. 8. Strengthen body immunity
Radix Peucedani	Peucedanum root	Bitter, sour and slightly cold	1. Descend “qi” and expel phlegm. 2. Disperse wind heat. 3. Dilate coronary artery. 4. Inhibit influenza virus. 5. Relieve pain, tranquilliser
Radix Platycodi	Platycodon root	Bitter, sour, medium	1. Promote the dispersing function of the lungs, relieve sore throat. 2. Expel phlegm and evacuate pus. 3. Relieve cough. 4. Anti-inflammatory. 5. Tranquilliser, relieve pain and reduce fever. 6. Inhibit gastric juice secretion, anti-gastric ulcer. 7. Reduce blood sugar. 8. Reduce blood lipid
Rhizoma Zingiberis Recens	Fresh ginger	Pungent, slightly warm	1. Induce diaphoresis and relieve the symptoms. 2. Warm the mid section of the abdomen and alleviate vomiting. 3. Warm the lungs to arrest cough. 4. Reduce the poisonous effect of other herbs
Fructus Forsythiae	Forsythia fruit	Bitter, slightly cold	1. Clear away pathogenic fever from the body. 2. Treat boils and resolve masses. 3. Control influenza virus. 4. Resist bacteria. 5. Reduce diuresis. 6. Resist hepatic injury. 7. Relieve vomiting
Radix Isatidis	Isatis root	Bitter, cold	1. Clear away heat and toxic material. 2. Remove pathogenic heat from blood and relieve sore throat. 3. Resist virus. 4. Resist bacteria
Radix Puerariae	Pueraria root	Sweet, pungent and cool	1. Reduce fever. 2. Stimulate the rash of measles to appear on surface of skin. 3. Control diarrhoea. 4. Relieve spasms. 5. Invigorate vital function and promote the production of body fluid. 6. Reduce blood pressure. 7. Relieve coro-

Table 1. Medicinal herbs for influenza (Continued)

			nary heart disease and angina pectoris. 8. Improve cerebral circulation
Folium Mori	Mulberry leaf	Bitter, sweet and cold	1. Expel wind and clear heat from the lungs. 2. Clear the liver and the eyes. 3. Remove heat from blood to arrest bleeding. 4. Restrain and kill bacteria. 5. Lower blood pressure, reduce blood lipid
Flos Chrysanthemi	Chrysanthemum	Pungent, sweet, bitter and slightly cold	1. Disperse wind and clear heat. 2. Clear away liver heat and brighten the eyes. 3. Restrain and kill bacteria, anti-inflammation. 4. Increase volume of blood flow of coronary artery. 5. Increase oxygen consumption of heart. 6. Reduce blood pressure
Fructus Arctii	Chrysanthemum	Pungent, bitter, and cold	1. Disperse wind heat. 2. Reduce fever and relieve swelling. 3. Benefit the throat. 4. Stimulate rashes to appear on surface of skin

Why it is important to do this review

A number of clinical trials of Chinese medicinal herbs for influenza have been conducted. The quality and effects of all these trials have not yet been assessed and systematically reviewed. Natural medicinal herbs are potential drug resources and the therapeutic and toxic effects of medicinal herbs need to be identified through a systematic review. Hundreds of millions of dollars are spent treating influenza annually in China, ensuring that a systematic review on the effectiveness of these medicinal herbs will be extremely useful in health policy planning.

This review summarises the existing evidence of comparative effectiveness and safety of medicinal herbs for preventing and treating influenza, according to current clinical trials.

OBJECTIVES

- To assess the effectiveness of Chinese medicinal herbs in treating uncomplicated influenza.

- To assess the effectiveness of Chinese medicinal herbs in preventing cases of influenza.

- To estimate the frequency of adverse effects associated with Chinese medicinal herbs for influenza.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials were included. If random allocation was indicated in a trial but randomisation procedure was not described, we telephone interviewed the primary author to ask for detailed information regarding the randomisation procedure. If the trial was quasi or falsely randomised (allocating patients by date of birth, date of admission, hospital number, alternation, or by the investigators' or patients' choosing, etc.), we excluded the trial. Trials not reporting our stated outcome measures were excluded.

Studies with a high percentage (more than 20%) of dropouts were also excluded.

Types of participants

People of all ages diagnosed with influenza by their clinical symptoms (for example, epidemic season, fever, myalgia, headache, cough, muscle aches and fatigue etc.) alone, or with laboratory evidence (relatively elevated lymphatic cell count in routine blood tests, influenza antigen detected in the patients' secretions, serum antibody reaction, RT-PCR positive results, or isolated influenza virus) should be included.

In prophylaxis studies, healthy people of all ages in an influenza epidemic area, should be included.

Patients with influenza complications such as otitis media, pneumonia, secondary bacterial infection, exacerbation of chronic respiratory disease, croup and bronchiolitis, and non-respiratory complications such as febrile convulsions, Reye's syndrome and myocarditis were excluded.

Types of interventions

Chinese medicinal herbs (including natural herbs and herbal products extracted from natural herbs) compared with placebo, no treatment, or chemical drugs normally used in care. Co-interventions were allowed if they were offered to both arms of the trial.

Types of outcome measures

1. The effectiveness rate of the drug.

- Rate of recovery: the symptoms and clinical manifestations were completely cleared and the body temperature returned to normal within one to three days after treatment.
- Marked improvement: most of the clinical symptoms had cleared and the body temperature returned to normal within one to three days.
- Partial improvement: part of the symptoms or manifestations of influenza neither improved nor worsened and the body temperature fell within three days.
- No improvement: symptoms or manifestations of influenza did not improve or may even have deteriorated (for example, complications may have occurred) after three days.

2. Duration for fever to clear or other symptoms to disappear or both.

3. Adverse effects: any adverse events such as malaise, nausea, fever, arthralgias, rash, headache and more generalised and serious signs resulting from the treatment that may lead to mortality, be life threatening, cause a toxic response, anaphylaxis, or discontinuation of treatment.

4. Incidence of influenza in prophylaxis studies.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, issue 1), which includes the Cochrane Acute Respiratory Infections Review Group specialised register; MEDLINE (January 1966 to January 2007); EMBASE (January 1988 to January 2007); CBM (Chinese Biomedical Database) (January 1980 to January 2007); and the Chinese Cochrane Center's Controlled Trials Register (up to January 2007). A comprehensive and exhaustive search strategy was formulated in an attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress), using the following terms in combination with the search strategy defined by the Cochrane Collaboration and detailed in Appendix 5c of the Cochrane Reviewers' Handbook (Edition 4.0) (Alderson 2004). The search string was adapted for other databases.

MEDLINE (OVID)

1 exp INFLUENZA/

2 influenza.mp.

3 or/1-2

4 exp Medicine, Chinese Traditional/

5 exp Medicine, Oriental Traditional/

6 exp Drugs, Chinese Herbal/

7 exp Plants, Medicinal/

8 chinese herb\$.mp.

9 (chinese adj medic\$).mp.

10 (medicin\$ adj herb\$).mp.

11 or/4-10

12 3 and 11

After scanning the full articles, we excluded studies which were not RCTs or clinical trials.

We also searched databases of ongoing trials: Current Controlled Trials (www.controlled-trials.com); and The National Research Register (<http://www.update-software.com/National/>).

Searching other resources

We attempted to identify additional studies by searching the reference lists of relevant trials, reviews, conference proceedings, and journals. In particular, with respect to journals, we searched those not indexed in the electronic databases.

Organisations (including the WHO), individual researchers working in the field, and medicinal herbal manufacturers were contacted in order to obtain additional references, unpublished trials, ongoing trials, confidential reports and raw data of published trials.

Data collection and analysis

Quality assessment of trials

The reporting quality of each trial was assessed, based largely on the quality criteria specified by Schulz and by Jadad (Jadad 1996; Schulz 1995). In particular, we studied the following factors.

1. Generation of the allocation sequence: an allocation sequence generated from a random numbers table, calculator or computer random-number generator was considered a real randomised RCT. Methods of allocating participants according to the date of birth, their hospital record number, the date to which they were invited to participate in the study, and so on, were considered inadequate.
2. Allocation concealment: use of a central independent unit, opaque sealed envelopes, or similar were considered adequate. Inadequate methods included those not described, an open table of random numbers or similar.
3. Double blinding: blinding of participants and investigators. Not performing double-blinding or inconsistency in the deliverance method (for example, tablets versus injections) was considered inadequate.
4. Follow up: number of and reasons for dropouts and withdrawals described were adequate; number of and reasons for dropouts and withdrawals not described were considered inadequate.

Based on these criteria, studies were broadly subdivided into the following three categories:

A - All quality criteria met: low risk of bias.

B - One or more of the quality criteria only partly met: moderate risk of bias.

C - One or more criteria not met: high risk of bias (Higgins 2005). This classification was used as the basis for a sensitivity analysis. Additionally, we explored the influence of individual quality criteria in a sensitivity analysis. Two review authors independently assessed each trial (XC, TW). Internal agreement was calculated using the kappa statistic, and disagreements were resolved by discussion, or by recourse to a third review author (GL). In cases of disagreement, the other review authors were consulted and a judgement was made, based on a consensus.

Data analysis

Data of some medicinal herbs were to be included in a meta-analysis if possible.

We had decided in advance that a quantitative meta-analysis should be performed when data of an outcome measure of similar intervention (same herbal preparation or same main components of a herbal preparation) in more than two included studies were available. The data should be dichotomous or continuous and be expressed as relative risk (RR) or mean difference (MD), respectively. The overall effect should be tested by using Z score with significance being set at $P < 0.05$. Heterogeneity should be tested for using the chi-squared statistic and I square (I^2) with significance being set at $P < 0.1$. Possible sources of heterogeneity should be assessed by sensitivity and subgroup analyses as described below. A fixed-effect model should be used when the studies in the subgroup were sufficiently similar ($P > 0.10$, $I^2 < 50$). A random-

effects model should be used in the summary analysis when there was heterogeneity between the subgroups. Publication bias should be tested for by using the funnel plot or other corrective analytical method, depending on the number of clinical trials included in the systematic review.

We did not find more than two studies using similar interventions in the treatment groups and consequently, we did not use a meta-analysis to calculate the pooled effect size. Data for each study were analysed and expressed as relative risks. The number of dropouts and the number of subjects who were lost to follow up for each study were summarised, when available, using an intention-to-treat analysis. When different herbal preparations (as intervention) in the treatment groups were considered as a whole, and then compared to certain chemical drugs in the control groups, the therapeutic effect was assessed by a qualitative analysis.

Selection of studies

We scanned the titles, abstract sections and keywords of every record retrieved. Full articles were located for further assessment when the information given suggested that the study: (1) included patients with uncomplicated influenza; (2) compared Chinese medicinal herbs with placebo or other active chemical drugs; (3) assessed one or more relevant clinical outcome measure; (4) used random allocation for the comparison groups.

If there was any doubt regarding these criteria from the information given in the title and abstract, we retrieved the full article for clarification. Inter-rater agreement for study selection was measured using the kappa statistic (Cohen 1960). If differences in opinion existed, we resolved these by discussion.

Data extraction and management

Two review authors (XC, TW) independently extracted data concerning details of the study population, interventions and outcomes using a standard data extraction form, specifically designed for this review. We abstracted data on participants, interventions, and outcomes, as described above. The data extraction form included the following items:

1. General information: published/unpublished, title, authors, reference/source, contact address, country, urban/rural etc., publication language, year of publication, duplicate publications, sponsor, and setting.
2. Trial characteristics: design, duration of follow up, method of randomisation, allocation concealment, blinding (patients, people administering treatment, outcome assessors), check of blinding.
3. Intervention(s): placebo included, intervention(s) (dose, route, timing), comparison intervention(s) (dose, route, timing), co-medication(s) (contents, dose, route, timing).
4. Patients: sampling (random/convenience), exclusion criteria, total number and number in comparison groups, sex,

age (children/adults), baseline characteristics, duration of influenza, diagnostic criteria, similarity of groups at baseline (including any co-morbidity), assessment of compliance, withdrawals/losses to follow up (reasons/description), subgroups.

5. Outcomes: outcomes specified above, any other outcomes assessed, other events, length of follow up, quality of reporting of outcomes.

6. Results: for outcomes and times of assessment (including a measure of variation), if necessary converted to measures of effect specified below, intention-to-treat analysis.

We resolved differences in data extraction by consensus, and with reference to the original article. If necessary, we sought information from the authors of the primary studies. We managed to contact authors by letter or telephone regarding missing information and confusing points such as methods of randomisation and allocation concealment; separate information for certain patient subgroups; information about complications; and number of dropouts. We managed to contact manufactures regarding the components of processed Chinese medicines if the components were unclear. Two review authors (XC, WT) independently extracted the original trial results. Disagreements were resolved by discussion, or in consultation with a third review author (GL). For binary outcomes, we extracted the number of events and total number in each group. For continuous outcomes we extracted the mean, standard deviation and sample size from each group.

Subgroup analysis and investigation of heterogeneity

If suitable trials are found in the future, we will perform the following subgroup analysis in order to explore the effect of size differences:

1. Adults versus children.
2. Intervention - different comparisons of formulations between studies, different administration routes (oral or intravenous), or doses (low and high, based on data).
3. Timing of outcome measures.

Sensitivity analysis

If suitable trials are found in the future, we will perform the following sensitivity analyses in order to explore the influence of the following factors on effect size:

1. Repeating the analysis excluding unpublished studies (if there were any).
2. Repeating the analysis taking into account the study quality, as specified above.
3. Repeating the analysis excluding any very long or large studies to establish how much they dominated the results.
4. Repeating the analysis excluding studies using the following filters: diagnostic criteria, publication language, funding source (industry versus other), and country.

The robustness of the results will be tested by using different measures of effect size (risk difference, odds ratio, etc) and different statistical models (fixed- and random-effects models), if necessary.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Included studies

Two trials were identified as true RCTs and fulfilled our inclusion criteria (Shi 2004; Xue 1999). Of the included trials, one (Shi 2004) was a treatment trial and the other trial (Xue 1999) was a prophylaxis and treatment trial. The information on herbal preparations for each trial including excluded trials and trials awaiting assessment are described in [Table 2](#).

Table 2. The composition of preparations of TCMs

Study ID	TCMs preparation	English TCM name	Pinyin TCM name
Yao 2003	Modified Ganlu Xiaodu Dan	Blackberrykiky Rhizome 10 g, Drug Sweetlad Rhizome 10 g, Sichuan Fritillaria bulb 10 g, Scutellaria Root 10 g, Villous Amomum Fruit 6 , Virgate Wormwood Herb 30 g, Weeping Forsythia Capsule 10 g, Peppermint 10 g, Bentong 10 g, Liuyisan 15 g, Fortune Eupatorium Herb 10 g, Indigowoad Root 30	Shegan 10 g, Changpu 10 g, Chuanbei 10 g, Huangqin 10 g, Sharen 6 , Yinchen 30 g, Lian-qiao 10 g, Bohe 10 g, Bentong 10 g, Liuyisan 15 g, Peiian 10 g, Banlangen 30 g, Daqingye 30 g

Table 2. The composition of preparations of TCMs (Continued)

		g, Indigowoad Leaf 30 g	
Yuan 2003	Jiang Fang Yin Qiao Tang	Fineleaf Schizonepeta Herb 10 g, Divaricate Saposhnikovia Root 10 g, Honeysuckle Flower 15 g, Weeping Forsythiae capsule 15 g, Incised Notopterygium Rhizome 10 g, Red Thorowax Root 15 g, Platycodon Root 10 g, Whiteflower Hogfennel Root 10 g, Peppermint 5 g, Kudzuvine Root 10 g, Indigowoad Leaf 15 g, Fresh Liquorate Root 5 g	Jingjie 10 g, Fangfeng 10 g, Yinhua 15 g, Lianqiao 15 g, Qianghuo 10 g, Chaihu 15 g, Jiegeng 10 g, Qianhu 10 g, Bohe 5g, Gegen 10 g, Daqingye 15 g, Shenggancao 15 g
Jiang 1981	Baihua Baijiang Chongji	Whiteflower Patrinia Herb	Baijiangcao
Xue 1999	Ganmao Capsule	Japanese Honeysuckle stem, Baical Skullcap Root, Platycodon Root, Bitter Apricot Seed, Fineleaf Schizonepeta Herb, Divaricate Saposhnicovia Root, Fresh Liquoric Root	Rendongteng, Huangqi, Jiegeng, Xingren, Jingjie, Fangfeng, Shenggancao
Wang 2001	Modified Qiang Bang Pu Bo Tang he Chai Pin Tang	Incised Notopterygium Rhizome, Great Burdock Achene, Mongolian Dandelion Herb, Peppermint, Red Thorowax Root, Baical Skullcap Root, Pinellia Tuber, Tangerine Peel, Swordlike Atractylodes Rhizome, Official Magnolia Bark	Qianghuo, Niubangzi, Pugongying, Bohe, Chaihu, Huangqin, Banxia, Chenpi, Cangshu, Houpu
Wang 2001	Qing Kai Ling	Cholic acid, Nacre, Hyodeoxycholic acid, Cape Jasmine Fruit, Buffalo Horn, Indigowoad Root, Baical Skullcap Root, Honeysuckle flower	Danshuan, Zhenzumu, Zhu Quyang Dansuan, Zhizi, Shuiniujiao, Banlangen, Huangqingan, Jinyinhua
Yu 2000	Liugan Heji	Fineleaf Schizonepeta Herb 10 g, Divaricate Saposhnikovia Root 10 g, Honeysuckle Flower 15 g, Weeping Forsythiae capsule 15 g, Incised Notopterygium Rhizome 10 g, Red Thorowax Root 15 g, Platycodon Root 10 g, Whiteflower Hogfennel Root 10 g, Peppermint 5g, Kudzuvine Root 10 g, Indigowoad Leaf 15 g, Fresh	Jinyinhua 15 g, Lianqiao 15 g, Banlangen 20 g, Daqingye 20 g, Jingjie 10 g, Fangfeng 10 g, Sangye 10 g, Shigao 30 g, Huangqin 12g, Jiegeng 10 g, Xingren 10 g, Gancao 10 g

Table 2. The composition of preparations of TCMs (Continued)

		Liquorate Root 5g	
Yu 2000	Fufang Daqingye	Indigowoad leaf, Honeysuckle Flower, Incised Notopterygium Rhizome, Bistort Rhizome, Rhubarb	Daqingye, Jinyinhua, Qianghuo, Quanshen, Dahuang
Du 1991	Bo Hao Sanhua Yin	Peppermint 10 g, Sweet Wormwood Herb 10 g, Honeysuckle Flower 10 g, Chrysanthemum 10 g, Common Goldenrod Herb 10 g, Cassia Twig 2 g	Bohe 10 g, Qinghao 10 g, Yinhua 10 g, Juhua 10 g, Yizhihuanghua 10 g, Guizhi 2 g
Yang 2000b	Chai Ge Jieji Tang Jiawei	Red Thorowax Root 10 g, Kudzu Root 30 g, Incised Notopterygium Rhizome 30 g, Platycodon Root 12 g, Crude Gypsum 30 g, Baical Skullcap Root 12g, White Paeony Root 10 g, Dahurian Angelica Root 12g, Weeping Forsythia Capsule 30 g, Divaricate Saposhnikovia Root 10 g, Tangerine Peel 10 g, Licorice Root 10 g, Fresh Ginger 6 g, Chinese Date 10 g	Chaihu 10 g, Gegen 30 g, Qianghuo 30 g, Jiegeng 12 g, Shengshigao 30, Huangqin 12g, Baishao 10 g, Baizhi 12g, Lianqiao 30 g, Fangfeng 10 g, Chenpi 10 g, Gancao 10 g, Shengjiang 6, Dazao 10 g
Zhang 2002	Chaihu Guizhi Tang Jiawei Fang	Red Thorowax Root, Pinellia Tuber, Cassia Twig, Baical Skullcap Root, Ginseng, Peony Root, Chinese Date, Fresh Ginger, Licorice Root	Chaihu, Banxia, Guizhi, Huangqin, Renshen, Shaoyao, Dazao, Shengjiang, Gancao
Hou 2002	Shuang Jie Tang	Crude Gypsum 30 g, Common Anemarrhena Rhizome 10 g, Honeysuckle Flower 30 g, Weeping Forsythia Capsule 10 g, Fine-leaf Schizonepeta Herb 6, Peppermint 6, Antelope Horn Powder 0.3g, Red Thorowax Root 10 g, Great Burdock Achene 10 g, Mulberry Twig 10 g, Reed Rhizome 60g, Fresh Licorice Root 6	Shengshigao 30 g, Zhimu 10 g, Jinyinhua 30 g, Lianqiao 10 g, Jingjiehui 6, Bohe 6, Lingyangjiaofen 0.3g, Chaihu 10 g, Niubangzi 10 g, Sangzhi 10 g, Lumaogen 60g, Shenggancao 6
Xu 2001	Da Qing Long Tang	Grilled Ephedra Herb 10 g, Cassia Twig 10 g, Gypsum 30 g, Apricot Seed 12 g, Grilled Licorice Root, 3 pieces of Ginger, 10 Chinese Dates	Zhimahuang 10 g, Guizhi 10 g, Shigao 30 g, Xingren 12 g, Zhigancao 6, 3 pieces of Shengjiang, 10 Dazao

Table 2. The composition of preparations of TCMs (Continued)

Shi 2004	E Shu You Zedoary	Zedoary	Ezhu
Hamazaki 2006	Bu Zhong Yi Qi Tang	Membranous Milkvetch Root / Mongolian Milkcatch Root, Gingseng, Liquoric Root, Large-head Atractylodes Rhizome, Chinese Angelica, Tangerine Peel, Chinese Thorowax Root /Red Thorowax Root, Large-trifolious Bugbane Rhizome	Huangqi, Renshen, Gancao, Baizhu, Danggui, Chenpi, Shengma, Chaihu
Hang 1998	Yuxingcao Koufu Ye	Heartleaf Houttynia Herb, Baical Skullcap Root, Indigowoad Root, Weeping Forsythiae Capsule, Honeysuckle Flower	Yuxingcao, Huangqin, Banlangen, Lianqiao, Jinyinhua
Huang 2003, Liu 2002	Yuxingcao injection	Extract from Heartleaf Houttynia Herb for injection	Yuxingcao
Jiang 2003	Yinhua Jiedu Granule	Honeysuckle Flower, Sweet Wormwood Herb, Fineleaf Schizonepeta Herb, Peppermint, Wild Chrysanthemum	Jinyinhua, Qinghao, Jingjie, Bohe, Yejuhua
Jin 1998	Shouqi Jiedu Decoction	Chinese Thorowax Root /Red Thorowax Root 15g, Honeysuckle Flower 15g, Cyrtomium Rhizome 15g, Sweet Wormwood Herb 10 g, Baical Skullcap Root 10 g, Baical Skullcap Root 20 g, Gypsum 30 g, Reed Rhizome 30 g, Raw Liquoric Root 6 g	Chaihu 15g, Yinhua 15g, Guanzhong 15g, Qinghao 10g, Huangqin 10g, Daqingye 20g, Shengshigao 30g, Lugan 30, Shenggancao 6g
Li 2005	Chuan Hu Ning injection	Extract from Common Andrographis Herb for injection	Chuanxinlian
Li 2005	San Shi decoction	Raw Gypsum, Gypsum Calcite, Talc Talcum, Ricepaperplant Pith, Apricot Seed, Lalang Grass Rhizome, Honeysuckle Flower, Weeping Forsythiae Capsule, Lotus Leaf, Indigowoad Root, Liquoric Root	Shengshigao, Hanshuishi, Huashi, Tongcao, Xingren, Maogen, Jinyinhua, Lianqiao, Heye, Banlangen, Gancao

Table 2. The composition of preparations of TCMs (Continued)

Lu 2004	Shuanghuanglian Kou Fu Ye	Hon- eysuckle Flower, Baical Skullcap Root, Weeping Forsythiae Cap- sule	Jinyinhua, Huangqin, Lianqiao
Qu 2005	Tan Re Qing injection	Baical Skullcap Root, Bear Gall Powder, Antelope Horn, Honeysuckle Flower, Weeping Forsythiae Capsule	Huangqin, Xiongdanfen, Shanyangjiao, Yinhua, Lianqiao
Yang 2000a	Redu Jing Kou Fu Ye	Membra- nous Milkvetch Root , Natural Indigo, Redroot Gromwell Root, Root Bark of Peony Tree, Baical Skullcap Root, Zedoary, Chinese Angelica, Peach Seed	Huangqi, Qingdai, Zhicao, Danpi, Huangqin, Eshu, Danggui, Taoren
Yang 2005a, Yang 2005b	Lianhuaqingwen capsule	Weeping Forsythiae Capsule, Honeysuckle Flower, Ephedra Herb, Male Fern Rhizome, Indi- gowoad Root, Gypsum, Pep- permint, Wrinkled Gianthys- sop Herb, Rhodiola quadri- fida, Heartleaf Houttuynia Herb, Rhubarb, Bitter Apricot Seed, Liquoric Root	Lian- qiao, Jinyinhua, Zhimahuang, Mianmaguanzhong, Banlangen, Shigao, Bohenaio, Guanghuox- iang, Hongjingtian, Yuxingcao, Dahuang, Chaokuxingren, Gan- cao
Zeng 2004	Yinma mixture	Honeysuckle Flower 15 g, Ephedra Herb 10 g, Weep- ing Forsythiae Capsule 15 g, Bit- ter Apricot Seed 10 g, Platycodon Root 10 g, Great Burdock Ach- ene 15 g, Peppermint 12 g, Ci- cada Slough 15 g, Baical Skullcap Root 12 g, Raw Gypsum 80 g, Cape Jasmine Fruit 15 g, Chinese Wolfberry Root-bark 15 g, Red Thorowax Root 15 g, Liquoric Root 6 g, Indigowoad Leaf 20 g	Yinhua 15 g, Mahuang 10 g, Lianqiao 15 g, Xingren 10 g, Ju- geng 10 g, Niubangzi 15 g, Bohe 12 g, Chantui 15 g, Huangqin 12 g, Shengshigao 80 g, Zhizi 15 g, Digupi 15 g, Chaihu 15 g, Gan- cao 6 g, Daqingye 20 g
Zhang 2000, Zhang 2004	Yiqi Qingjie Fa (Influenza No. 1)	Manyflower Solomonseal Rhi- zome, Fragrant Solomonseal Rhi- zome, Pinellia Tuber, Red Thorowax Root, Com- mon Hongfennel Root, Platy- codon Root, Great Burdock Achene, Baical Skullcap Root, Raw Liquoric Root, Indigowoad	Huangjing, Yuzhu, Banxia, Chaihu, Qianhu, Jugeng, Niubangzi, Huangqin, Shenggancao, Banlangen, Jinyin- hua, Xuanshen

Table 2. The composition of preparations of TCMs (Continued)

		Root, Honeysuckle Flower, Figwort Root	
Zhang 2005	Gan Qing Dai Paoji	Capsule, Raw Gypsum, Baical Skullcap Root, Figwort Root, Red Thorowax Root, Large leaf Gentian Root, Platycodon Root, Apricot Seed, Thunberg Fritillary Bulb, Common Coltsfoot Flower, Indigowoad Root, Cicada Slough, Peppermint, Liquoric Root	Jinyinhua, Lianqiao, Shengshigao, Huangqin, Xuanshen, Chaihu, Qinghao, Qinjiao, Jugeng, Xingren, Zhemubei, Kuandonghua, Banlangen, Chanyi, Bohe, Gancao
Zhao 2006	kang liu gan he ji	Peppermint 9 g, Golden Thread 9 g, Weeping Forsythiae Capsule 10 g, Fine leaf Schizonepeta Herb 10 g, Sweet Wormwood Herb 10 g, Indigowoad Root 10 g, Indigowoad Leaf 10 g, Red Thorowax Root 10 g, Baical Skullcap Root 10 g, Membranous Milkvetch Root 15 g, Ephedra Herb 6 g, Ovientvine 12 g, Heartleaf Houttuynia Herb 30 g	Bohe 9 g, Huanglian 9 g, Lianqiao 10 g, Jingjie 10 g, Qinghao 10 g, Banlangen 10 g, Daqingye 10 g, Chaihu 10 g, Huangqin 10 g, Huangqi 15 g, Mahuang 6 g, Qingfengteng 12 g, Yuxingcao 30 g
Zhong 2005	Lu Qing granule	Antelope Horn Powder, Gypsum, Common Anemarrhena Rhizome, Reed Rhizome, Indigowoad Root, Red Paeony Root, Rhubarb, Forbes Notopterygium Rhizome, Sweet Wormwood Herb, Honeysuckle Flower, Weeping Forsythiae Capsule, Chinese Mosla Herb, Indigowoad Leaf	Linyangjiaofen, Shigao, Zhimu, Lugen, Banlangen, Chishao, Dahuang, Qianghuo, Qinghao, Jinyinhua, Lianqiao, Xiangru, Daqingye
Qiu 1997	Mixture of Xiao Chaihu decoction, Zhizi Gu decoction and Biyu Shan	Red Thorowax Root 10 g, Fermented Soya Beans 10 g, Pinellia Rhizome 10 g, Silkworm Feculae 10 g, Baical Skullcap Root 10 g, Raw Cape Jasmine Fruit 10 g, Jasper Powder 10 g, Danshen Root 10 g, 5 Chinese Dates	Chaihu 10 g, Dougu 10 g, Fabanxia 10 g, Chansha 10 g, Huangqin 10 g, Shengshanzhi 10 g, Biyusan 10 g, Dangshen 10 g, 5 Dazhao
Song 2002	Shubiao Jiedu Yin	Indigowoad Root 30 g, Honeysuckle Flower 30 g, Vietnamese Sophora Root 15 g, Kudzuvine Root 15 g, Thunberg Fritillary	Banlangen 30 g, Erhua 30 g, Shandougen 15 g, Gegen 15 g, Zhebeimu 15 g, Qianghuo 10 g, Huangqin 9 g, Niubangzi 12 g,

Table 2. The composition of preparations of TCMs (Continued)

		Bulb 15 g, Incised Notopterygium Rhizome 10 g, Baical Skullcap Root 9 g, Great Burdock Achene 12 g, Cyrtomium Rhizome 12 g, Peppermint Leaf 6 g, Platycodon Root 8 g, Weeping Forsythiae Capsule 20 g	Guanzhong 12 g, Boheye 6 g, Jugeng 8 g, Lianqiao 20 g
Li 2001	Zhongyi Fang Ji	Raw Gypsum 30 g, Common Anemarrhena Rhizome 15 g, Red Thorowax Root 12 g, Baical Skullcap Root 9 g, Cape Jasmine Fruit 12 g, Fine leaf Schizonepeta Herb 15 g, Peppermint 6 g, Raw Licorice Root 6 g	Shengshigao 30 g, Zhimu 15 g, Chaihu 12 g, Huangqin 9 g, Zhizi 12 g, Jingjie 15 g, Bohe 6 g, Shenggancao 6 g

Designs of included studies

Details of the included studies are shown in the 'Characteristics of included studies' table. Both the included studies were randomised controlled, parallel designed studies.

Participants of included studies

The number of participants in the two included studies were 61 and 951 respectively, totaling 1012 participants. In the Shi 2004 trial, participants were children aged 6 to 10, clinically diagnosed with influenza B in an epidemic area. Disease duration was less than 17 hours. Laboratory tests excluded a bacterial infection. In the Xue 1999 trial, participants were healthy people as well as participants clinically diagnosed with influenza A3/H3N2 within two days of disease onset in an epidemic area.

In the Xue 1999 trial statistical analyses for prevention and treatment were performed separately. Those who subsequently developed influenza in the prevention study were eventually included in the treatment analyses.

Interventions of included studies

The interventions in both trials were Chinese medicinal herbs compared with antiviral drugs. In the Shi 2004 trial, volatile oil extracted from Zedoary was compared with ribavirin plus vitamin C for injection, used for three to five days, with the antibiotic erythromycin given to both arms for preventing secondary bacterial infection. In the Xue 1999 trial, compound herbal preparations were compared with amantadine, both taken in capsular form for seven days, for either the prophylaxis or treatment study.

Outcome measures of included studies

One trial (Shi 2004) assessed the rate of effectiveness at the end of day three, following treatment, as the outcome (recovery/marked improvement/partial improvement/no improvement), according to the defervescence period, the period and extent of symptoms alleviation. Adverse reactions in the gastrointestinal tract were reported in both trial arms. The other trial (Xue 1999) assessed the incidence of influenza at the end of day seven following treatment, as the outcome for the prophylaxis study; and rate of recovery and inefficacy at the end of day two after treatment, as the outcome for the treatment study. Inefficacy was defined as effectiveness other than recovery in this study, which covered marked improvement, partial improvement and no improvement as regulated in our review. Adverse reactions in the gastrointestinal tract were mentioned in the control group but no data were reported. Neither study took duration for fever clearance or other symptom alleviation or both as outcome measures.

Excluded studies

A total of 35 trials claiming to be RCTs were retrieved. Of these, 30 trials were excluded due to the following reasons (see 'Characteristics of excluded studies' table): the interventions were one Chinese medicinal herb compared to another, with or without chemical drugs added in one arm in 13 trials (Jiang 2003; Wang 2001; Yang 2000b; Yang 2005a; Yang 2005b; Yu 2000; Zeng 2004; Zhang 2000; Zhang 2002; Zhang 2004; Zhang 2005; Zhao 2006; Zhong 2005); four trials did not provide the data to meet the outcome criteria (Hamazaki 2006; Hang 1998; Lindenmuth 2000; Lu 2004);

participants in four trials experienced complications (Jin 1998; Li 2005; Liu 2002; Zeng 2004); and one trial used a Japanese herbal medicine as the intervention (Kubo 2007). We then conducted telephone interviews with the authors of the remaining 14 trials to obtain the information of randomisation procedure and found 9 trials were actually false or quasi RCTs (Du 1991; Hou 2002; Huang 2003; Li 2001; Qu 2005; Xu 2001; Yang 2000a; Yao 2003; Yuan 2003). We failed to contact the authors of three trials which are listed in the 'Studies awaiting assessment' (Qiu 1997; Song 2002; SRCG 1981).

Risk of bias in included studies

Randomisation

Shi (Shi 2004) stated that the statistical software package New Drug Statistical Treatment (NDST) was used to generate the allocation sequence. Xue (Xue 1999) mentioned random allocation but did not give a description. After conducting a telephone interview with the trial author, we learned that the allocation sequence was generated by computer software.

Description of withdrawals and losses to follow up and intention-to-treat analysis

Neither of the included studies mentioned dropouts or performed an intention-to-treat analysis.

In the Xue 1999 trial, there were 519 participants in the intervention group and 432 in the control group. It is unclear whether the imbalance of participant numbers in the two arms were produced by inadequate randomisation or withdrawals during follow up, or for another reason. However, the trial author did not give us a satisfactory answer, as he could not remember the details. Both included studies were considered at high risk for bias and graded as category C.

Allocation

Neither of the included trials mentioned allocation concealment, after conducting telephone interviews with the trial authors, we learned that one Shi 2004 did not perform allocation concealment and Xue 1999 used an adequate allocation concealment generated by a central computer.

Blinding

Shi (Shi 2004) did not mention blinding, but after contacting the trial author by telephone, we learned that no blinding was used. Xue (Xue 1999) mentioned double-blinding. Neither the participants nor the conductors knew which interventions were administered. The drugs in the two arms were the same in appearance, route and schedule, to ensure blinding.

Effects of interventions

It was not possible to combine the results of the studies in a meta-analysis due to clinical heterogeneity. Therefore, the results are presented as separate RR for each study. Planned subgroup/sensitivity analyses were not performed.

Recovery

E Shu You (volatile oil extracted from Zedoary) showed a better result, without significant difference, than ribavirin for recovery within three days of treatment (Shi 2004: RR 2.18, 95% confidence interval (CI) 0.87 to 5.43), and Ganmao Capsule showed a significantly better result than amantadine for recovery within two days of treatment (Xue 1999: RR 5.17, 95% CI 3.82 to 6.99).

Marked improvement

Only one study (Shi 2004) provided data for analysis of marked improvement with no significant difference between E Shu You and ribavirin in the treatment of influenza (RR 1.02, 95% CI 0.45 to 2.29).

Partial improvement

Data for analysis of partial improvement was available in one study (Shi 2004) and showed no significant difference between E Shu You and ribavirin in the treatment of influenza (RR 0.91, 95% CI 0.36 to 2.27).

No improvement

Xue 1999 assessed the therapeutic effect with the outcome measures recovery and inefficacy at the end of two days of treatment. In this case, inefficacy covered marked improvement and partial improvement as well as no improvement, which was defined differently from most of the studies and our review. Thus, the rate of no improvement as assessed in our review was not available in this study. In the other study (Shi 2004), E Shu You showed a lower rate of no improvement than ribavirin in the treatment of influenza, without a significant difference (RR 0.40, 95% CI 0.14 to 1.17).

Incidence of influenza

In the prophylaxis study (Xue 1999) influenza incidence was statistically significantly lower in the Ganmao capsule group than in the amantadine group, within seven days of treatment (RR 0.48, 95% CI 0.38 to 0.61).

Adverse reactions

Data for adverse reactions were available in one study (Shi 2004) and showed a non-statistically significant lower rate of adverse reactions in the gastrointestinal tract in the E Shu You group and ribavirin group (RR 0.58, 95% CI 0.09 to 3.73).

DISCUSSION

Summary of main results

Due to clinical heterogeneity, meta-analysis was not performed. Of the two included studies, only one indicated that compared with antiviral drugs, Chinese medicinal herbs may be effective in preventing influenza and alleviating influenza symptoms. However, the small number of participants and studies, together with the poor quality of this study, does not allow us to draw reliable conclusions.

Quality of the evidence

Since 2005, under the leadership of Professor Taixiang Wu from the Chinese Cochrane Centre, the review authors extensively investigated the methodological quality of over 3000 alleged RCTs by interviewing the primary trial authors by telephone. The results unexpectedly frustrated us in that only about 7% of the trials used correct randomisation methods. In this updated review, we made substantive changes by restricting the criteria for inclusion of studies: (1) excluding false or quasi-RCTs by interviewing the primary trial authors by telephone and asking about the randomisation procedures. In the original version of this review, we included studies that claimed to be RCTs, even when there were no descriptions about the generation of allocation sequence. After contacting the primary trial authors, we learned that the former version of this review was at a high-risk for bias in including non-randomised controlled trials, as these trials could yield larger estimates of treatment effect than those using a randomised allocation (Chalmers 1983). Quasi-randomisation is also associated with considerable bias due to a lack of allocation concealment (Altman 1991); (2) excluding studies comparing one Chinese medicinal herb with another. Numerous self-composed herbal preparations and patent herbal products are used for influenza in China, while no sufficient evidence can support their efficacy. When comparing two herbal medicines we remained unsure as to whether the relatively more effective herbal medicine was indeed efficacious against influenza. Thus, we excluded studies that used herbal medicines in the control group but kept the placebo or the normally used drugs as the control, such as antiviral and antipyretic-analgesic drugs. Most of the retrieved studies did not give adequate descriptions of the methodology used, which may have misled us if we had not clarified the details, for example, inclusion of non-RCTs and classifying the trials into category B rather than C. It was an exhausting but necessary process to interview every primary trial author before deciding whether to include these trials, when the methodological details were not reported. Contacting authors by telephone was more effective than writing to them because of a higher response rate and left no time for the trial authors to make up artificial details. However, even after confirmation of true randomisation, we found that the methodological quality of the studies remained poor.

Allocation concealment is an important marker of trial quality. In a study of 250 controlled trials from 33 meta-analyses in pregnancy and childbirth, investigators found that alleged RCTs with

inadequate and unclear allocation concealment yielded larger estimates of treatment effects (41% and 33%, respectively, on average) than trials in which authors reported adequate concealment (Schulz 1995). However, very few potential articles considered for our review reported or performed allocation concealment; one of the two included trials failed to perform allocation concealment, leading to high risk of selection and confounding bias.

In one of the included trials, no blinding was conducted with either the participants or the investigators, which led to a high risk of performance bias. None of the studies mentioned blinding to the outcome assessors, which promotes suspicion of detection bias. Publication bias may exist as all the included studies were published in Chinese and no primary articles reporting negative results were found. The huge difference in the number of participants between the two arms raised suspicion of inadequate randomisation or a significant number of withdrawals which may have led to high selection or attrition bias in one study (Xue 1999).

During the process of interviewing the trial authors, we understood that it was difficult for them to perform double-blinding because of certain features associated with Chinese medicinal herbs, for example, aroma and appearance. Capsules were used in one study (Xue 1999). Other methods included extracts from herbal medicines administered by injection by using an opaque cover around the fluid bag if the herb was of a particular colour. Many trials are conducted to assess the efficacy of a plant before making the expensive decision to produce it as a patented medicine and double-blinding is almost impossible.

All the patients in the included studies were diagnosed by epidemiology, clinical symptoms and routine tests. It is possible that participants with other acute respiratory infections such as the common cold not caused by the influenza virus may have been misdiagnosed as having influenza and were included in the trials. The disease duration on entry varied between the potential studies we retrieved for inclusion. Secondary bacterial infection or other complications that complicate influenza treatment may have been present, even if the trial authors did not find or report them.

In the practice of TCM, herbal preparations should match the type of 'zheng' which equates to a diagnosis. Trial authors are encouraged to explain each 'zheng' by using conventional medical terms, therefore making it more convenient for physicians and consumers to choose an appropriate preparation.

As for the interventions, we considered the commonly used antiviral and antipyretic-analgesic drugs as controls were acceptable. However, there is potential for bias. If the trial author knows that a 'positive' drug was used and the study was an 'equal effect test' study, there is a potential risk that the outcome detectors will consider similar results for the two groups. In this case, even double-blinding is useless. If it is a 'superior effect test', the trial authors tend to overestimate the effect in the treatment group if allocation concealment and blinding were inadequate. When a Chinese herbal medicine combined with a supposed 'positive' intervention is found to be more effective than the 'positive' drug alone for

influenza, this herbal medicine is considered effective. An alternative would be to compare Chinese medicinal herbs to a placebo (it is also recommended to compare first to placebo to test its effectiveness and subsequently to compare to another treatment that was tested against placebo and proved as effective), with another 'positive' drug given to both arms.

Although Chinese herbal medicines as a treatment for influenza and the method of manufacturing these medicines are widely accepted in China, most of the constituents of the pharmacologically prepared drugs used in trials cannot be specified. This is in marked contrast to the pharmacological agents used in Western medicine, for which the chemical constituents, their quantities, and the percentage of any impurities or contaminants are precisely known. In addition, the variation between different production batches of Western medicines is kept within specified limits. In contrast, variation between formulations and batches of pharmacological agents are inevitable in TCM, though the Chinese Government specifies the acceptable limits of variation. This variation is a factor that may contribute to any heterogeneity between different study results. The application of TCM signs is also limited as not every is familiar with them. However, one must accept that the overall treatment concept for TCM is different to that used in Western medicine.

The outcome definition and timing of measures varied between studies. The outcome measures, regulated by the primary version of this review, were based on a subjective assessment of defervescence and symptom withdrawal using dichotomous data. We may have missed additional information from studies which did not use the outcome measures stated in our original review. In this updated review, we added continuous data for duration of defervescence and symptom withdrawal, as well as influenza incidence in the prophylaxis studies. In one of the included studies (Shi 2004) ibuprofen was added temporally to patients with high fever, whereas no data was provided about how many participants in each group received the extra drug. This may have influenced the results.

TCM signs are important outcome measures in traditional practice. We will consider including TCM signs as a secondary or an additional outcome in the next update of this review. However, it is difficult to compare or quantify TCM signs as they have subjective outcomes. For example, 'mai xiang' equates to pulse presentations. Diagnosing 'mai xiang' in TCM is a complex and difficult technique, dependent on the TCM physician's experience. TCM researchers and physicians should find a gold standard method which is repeatable and easy to practice when measuring TCM signs.

In a timely effort, the Chinese Evidence-Based Medicine Centre of the Ministry of Health of the People's Republic of China, the Chinese Cochrane Centre, the Ministry of Education of Virtual Re-

search Centre of Evidence-Based Medicine, the Chinese Clinical Trial Register and the West China Hospital of Sichuan University, as well as 48 journals in China have taken the first step to issue the Joint Statement of Establishing Chinese Clinical Trial Registration and Publishing System, which will promote the transparency and quality of Chinese clinical trials. We hope that more journals and trials will join in this programme.

AUTHORS' CONCLUSIONS

Implications for practice

The present existing evidence is too weak to support or reject the use of any Chinese medicinal herbs for preventing or treating uncomplicated influenza.

Implications for research

More studies, performed worldwide, with high methodological quality, large numbers of participants and good reporting to provide stronger evidence are required. Information on conducting trials should be reported in detail according to CONSORT (Moher 2001). The establishment of the Chinese Clinical Trial Register and the issue of Joint Statement of Establishing Chinese Clinical Trial Registration and Publishing System have taken the first step to produce high quality clinical trials meeting international criteria. More journals and clinical trials should join in this programme. The intervention in the control group should be a placebo, no treatment or the commonly used antiviral and antipyretic-analgesic drug, but not herbal medicines or the combination of drugs plus herbal medicines, until proved as effective for influenza. Co-interventions given equally to both arms are acceptable. The disease duration on entry should be restricted and if economics permit, laboratory tests (routine blood tests, serum tests or pathogenic examinations) and chest X-rays should be conducted to define inclusion and exclusion criteria. Attention should also be paid to the definition of outcome measures and the incidence of adverse reactions.

ACKNOWLEDGEMENTS

The authors thank Elizabeth Dooley for assistance; Drs. Leonard Leibovici, Bob Douglas, Alyson Huntley, and Amy Kathleen Godfrey Arkle for helpful comments and advice for the primary version; and Ruth Foxlee for useful advice in constructing the search strategy. We finally wish to thank Anca Zalmanovici, Shirley Manknell, George Lewith, and Mark Jones for helpful comments and advice for this updated version.

REFERENCES

References to studies included in this review

Shi 2004 *{published data only}*

Shi XX, Chen MM. Clinical effect of E Shu You glucose injection in the treatment of type B influenza in children. *Zhong Guo Lin Chuang Yao Xue Za Zhi [Chinese Journal of Clinical Pharmacy]* 2004;**13**(1):38–40.

Xue 1999 *{published data only}*

Xue EB, Dong Z. Clinical observation of 519 influenza patients prevented and treated with Ganmao Jiaonang. *Tianjin Zhong Yi [Tianjin Journal of Traditional Chinese Medicine]* 1999;**16**(4):13–4.

References to studies excluded from this review

Du 1991 *{published data only}*

Du YL, Ma WM. 100 cases with influenza fever treated with Bo Hao Sanhua Yin. *Hebei Zhong Yi [Hebei Journal of Traditional Chinese Medicine]* 1991;**13**(5):6.

Hamazaki 2006 *{unpublished data only}*

Hamazaki K, Sawazaki S, Itomura M, Huan M, Shibahara N, Kawakita T, et al. No effect of a traditional Chinese medicine, Hochu-ekki-to, on antibody titer after influenza vaccination in men: A randomized, placebo-controlled, double-blind trial. *Phytomedicine* 2006;**24**:Epub ahead of print.

Hang 1998 *{published data only}*

Hang JZ. 96 children with influenza treated with Yuxingcao Koufu Ye Compound. *Zhejiang Zhong Yi Za Zhi [Zhejiang Journal of Traditional Chinese Medicine]* 1998;**33**(8):381.

Hou 2002 *{published data only}*

Hou YJ. Clinical observation of treating winter influenza with Traditional Chinese Medicine 'Shuang Jie Tang'. *Beijing Zhong Yi [Journal of Beijing University of Traditional Chinese Medicine]* 2002;**21**(4):231–2.

Huang 2003 *{published data only}*

Huang ZP. Effect analysis of Yu Xing Cao in the treatment of 46 cases with influenza. *Zhongguo Xin Yi Yao [China New Medicine]* 2003;**2**(3):63–4.

Jiang 2003 *{published data only}*

Jiang M, Xiong LL, Qi ZQ, Zou JD. Clinical trial for treating wind-heat syndrome of upper respiratory infection and influenza with Yinhuo Jiedu Granule. *Zhong Yao Xin Yao Yu Lin Chuang Yao Li [Traditional Chinese Drug Research & Clinical Pharmacology]* 2003;**14**(4):270–2.

Jin 1998 *{published data only}*

Jin Y. Clinical observation of treating influenza fever with Shouqi Jiedu Fa. *Xinjiang Zhong Yi Yao [Xinjiang Journal of Traditional Chinese Medicine]* 1998;**16**(1):18.

Kubo 2007 *{published data only}*

Kubo T, Nishimura H. Antipyretic effect of Mao-to, a Japanese herbal medicine, for treatment of type A influenza infection in children. *Phytomedicine* 2007;**14**(2-3):96–101.

Li 2001 *{published data only}*

Li YJ. Effect analysis of treating influenza fever with Chinese medicine and Western medicine. *Xian Dai Zhong Xi Yi Jie He Za*

Zhi [Modern Journal of Integrated Traditional Chinese and Western Medicine] 2001;**10**(3):214.

Li 2005 *{published data only}*

Li HG. Curative observation on summer severe influenza treated with Chuan Hu Ning injection plus San Shi decoction modified. *Zhong Guo Zhong Yi Ji Zheng [Journal of Emergency in Traditional Chinese Medicine]* 2005;**14**(6):543–5.

Lindenmuth 2000 *{published data only}*

Lindenmuth GF, Lindenmuth EB. The efficacy of echinacea compound herbal tea preparation on the severity and duration of upper respiratory and flu symptoms: a randomized, double-blind, placebo-controlled study. *Journal of Alternative and Complementary Medicine* 2000;**6**(4):327–34. [MEDLINE: 10976979]

Liu 2002 *{published data only}*

Liu JL, Wang XY. 80 cases of treating influenza pneumonia with Yuxingcao injection. *Liaoning Zhong Yi Za Zhi [Liaoning Journal of Traditional Chinese Medicine]* 2002;**29**:502.

Lu 2004 *{published data only}*

Lu ZQ. 246 cases of clinical observation on Shuanghuanglian Kou Fu Ye for cold. *Shenzhen Zhong Xi Yi Jie He Za Zhi [Shenzhen Journal of Integrated Traditional Chinese and Western Medicine]* 2004;**14**(6):368–70.

Qu 2005 *{published data only}*

Qu JL, Gao X, Zhou SF, Xu SP, Yu Y. Clinical effect of Tan Re Qing injection in the treatment of upper respiratory tract infection caused by type-A influenza. *Zhong Guo Zhong Yi Ji Zheng [Journal of Emergency in Traditional Chinese Medicine]* 2005;**14**(1):26–7.

Wang 2001 *{published data only}*

Wang SY. 100 children with influenza treated with Jianguo Pu Bo Tang he Chai Ping Tang. *Fujian Zhong Yi Yao [Fujian Journal of Traditional Chinese Medicine]* 2001;**32**(2):49–50.

Xu 2001 *{published data only}*

Xu J. Clinical observation of Da Qing Long Tang treating influenza fever. *Changchun Zhong Yi Xue Yuan Xue Bao [Academic Periodical of Changchun College of Traditional Chinese Medicine]* 2001;**17**(2):29–30.

Yang 2000a *{published data only}*

Yang CX, Yan TY. Clinical research on Redu Jing treating influenza-caused upper respiratory tract infection. *Beijing Zhong Yi [Journal of Beijing University of Traditional Chinese Medicine]* 2000;**19**(4):17.

Yang 2000b *{published data only}*

Yang H. 101 influenza patients treated with Chai Ge Jieji Tang Jiawei. *Zhong Guo Zhong Yi Ji Zheng [Journal of Emergency in Traditional Chinese Medicine]* 2000;**9**(3):132.

Yang 2005a *{published data only}*

Yang LB, Ji ZH, Wang BQ. Clinical observation of the therapeutic effect of Lianhuaqingwen capsule on 280 cases of influenza. *Yi Nan Bing Za Zhi [Journal of Difficult and Complicated Cases]* 2005;**4**(5):276–8.

Yang 2005b *{published data only}*

Yang LB, Ji ZH, Gao XD, Gu CH. Phase 2 clinical study of Lianhua Qingwen Capsule for influenza. *Zhong Yao Xin Yao Yu Lin*

Chuang Yao Li [Traditional Chinese Drug Research & Clinical Pharmacology] 2005;16(4):290–3.

Yao 2003 {published data only}

Yao WH, Zhou AG, Qu JH, Han X. Clinical analysis of treating influenza fever with modified Gan Lu Xiao Du Dan. *Yi Xue Yan Jiu Tong Xun [Bulletin of Medical Research]* 2003;32(5):64–5.

Yu 2000 {published data only}

Yu DC, Meng XF. 98 influenza patients treated with Liugan Heji. *Xian Dai Zhong Xi Yi Jie He Za Zhi [Modern Journal of Integrated Traditional Chinese and Western Medicine]* 2000;9(8):736.

Yuan 2003 {published data only}

Yuan XH, Liu B. 120 cases of treating winter influenza with Jing Fang Yin Qiao Tang. *Shi Yong Zhong Xi Nei Ke Za Zhi [Journal of Practical Traditional Chinese Internal Medicine]* 2003;17(3):191.

Zeng 2004 {published data only}

Zeng QX, Hu DZ. Clinical study on Yinma mixture in treating fever of Wenre influenza. *Zhongguo Zhong Xi Yi Jie He Ji Jiu Za Zhi [Chinese Journal of Integrated Traditional and Western Medicine in Intensive Critical Care]* 2004;11(3):176–8.

Zhang 2000 {published data only}

Zhang RW, Liu FL, Peng XJ, Gao GL. Treating influenza with Yiqi Qingjie Fa. *Shandong Zhong Yi Za Zhi [Shandong Journal of Traditional Chinese Medicine]* 2000;19(8):460–1.

Zhang 2002 {published data only}

Zhang XM, Jiang LD, Shang XZ, Zhang YS. Comparison of therapeutic effect between Chaihu Guizhi Tang Jiawei Fang Tangji and Chaihu Guizhi Tang Jiawei Fang Keliji. *Zhong Guo Zhong Xi Yi Jie He Ji Jiu Za Zhi [Chinese Journal of Integrated Traditional and Western Medicine]* 2002;11(3):174–5.

Zhang 2004 {published data only}

Zhang DN, Che SQ, Xu Y, et al. Self-composed herbal preparation of Influenza No.1 for 960 cases of influenza. *Shanxi Zhong Yi Za Zhi [Shanxi Journal of Traditional Chinese Medicine]* 2004;25(8):722–3.

Zhang 2005 {published data only}

Zhang SX, Chai JL. Gan Qing Dai Paoji for treating 60 cases of influenza. *Qilu Yao Shi [Qilu Pharmaceutical Affairs]* 2005;24(12):751–2.

Zhao 2006 {published data only}

Zhao DY. Clinical study on kang liu gan he ji for influenza. *Zhejiang Zhong Yi Za Zhi [Zhejiang Journal of Traditional Chinese Medicine]* 2006;41(6):326–7.

Zhong 2005 {published data only}

Zhong Q, Zhou HF, Lin K, Pang ZW, Chen N, Ning DX, et al. Clinical analysis of Lu Qing granule in the treatment of influenza. *Liaoning Zhong Yi Za Zhi [Liaoning Journal of Traditional Chinese Medicine]* 2005;32(7):628.

References to studies awaiting assessment

Qiu 1997 {published data only}

Qiu LY. Effect of integrated traditional Chinese medicine and Western medicine in the treatment of influenza fever in spring and summer. *Shi Yong Zhong Xi Yi Jie He Za Zhi [The Practical Journal of Integrating Chinese with Modern Medicine]* 1997;10(8):786–7.

Song 2002 {published data only}

Song GL. Clinical effect of Shubiao Jiedu Yin in the treatment of influenza. *Sichuan Zhong Yi [Journal of Sichuan Traditional Chinese Medicine]* 2002;20(10):28–9.

SRCG 1981 {published data only}

Scientific Research Collaboration Group (SRCG) for preventing and treating influenza in Yichun Area in Jiangxi Province. Effect observation of 401 influenza patients treated with Baihua Baijiang. *Zhong Ji Yi Kan [Chinese Journal of Medicine]* 1981;31(3):39–40.

Additional references

Ahmed 1996

Ahmed AH, Nicholson K. The efficacy of influenza vaccine. *Review in Medical Microbiology* 1996;7(1):23–30.

Alderson 2004

Alderson P, Green S, Higgins JPT, editors. Cochrane Reviewers' Handbook 4.2.2 [updated December 2003]. *The Cochrane Library, Issue 1*. Chichester, UK: John Wiley & Sons, Ltd, 2004.

Altman 1991

Altman D. Randomisation: essential for reducing bias. *BMJ* 1991;302:1481–2.

Buda 2000

Buda A, Alves de Cunha AJL. Amantadine and rimantadine for influenza A in children and the elderly. *Cochrane Database of Systematic Reviews* 2000, Issue 3. [DOI: 10.1002/14651858.CD002745.pub2]

CDC 2007

CDC. Influenza: The Disease. <http://www.cdc.gov/flu/about/disease.htm> (Accessed March 2007) 2007.

Cezanne 1997

Cezanne HH. Herbalism. <http://www.drcezanne.com/herbalism.htm> (Accessed 2003) 1997.

Chalmers 1983

Chalmers TC, Celano P, Sacks HS, Smith H. Bias in treatment assignment in controlled clinical trials. *New England Journal of Medicine* 1983;309:1358–61.

Claas 1998

Class EC, de Jong JC, van Beek R, Rimmelzwaan GF, Osterhaus AD. Human influenza virus, A/Hong Kong/156/97(H5N1) infection. *Vaccine* 1998;16(9-10):977–8.

Cohen 1960

Cohen J. A coefficient of agreement for nominal scales. *Educational and Psychological Measurement* 1960;20:37–46.

Deng 1998

Deng WL. In: Shen YJ editor(s). *Pharmacology of Traditional Chinese Medicine*. 1st Edition. Beijing: People Health Publishing House, 1998.

Fleming 1999

Fleming D, Zambon M, Waston J. Management of influenza. National Prescribing Center 1999.

HamiltonBaldwin 2000

Hamilton-Baldwin S. The flu: treatment and prevention. <http://www.ncpanet.org/CONTEdu/influenza.html> (Accessed 2003) 2000.

Higgins 2005

Higgins JPT, Green S, editors. Application of quality assessment criteria. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005], Section 6.9. Chichester, UK: John Wiley & Sons, Ltd, 2005, issue 3.

Hou 1995

Hou JY. *Contemporary Pharmacology of Traditional Chinese Medicine*. 1st Edition. Tianjin: Tianjin Scientific and Technological Publishing House, 1995.

Jadad 1996

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds JM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary?. *Controlled Clinical Trials* 1996;**17**:1–12.

Liu 2001

Liu GW. *Chinese Herbal Medicine*. 1st Edition. Beijing: Hua Xia Publishing House, 2001.

Moher 2001

Moher D, Schulz KF, Altman D. The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomized Trials. *Journal of the American Medical Association* 2001;**285**(15):1987–91.

Moscona 2005

Moscona A. Oseltamivir resistance - disabling our influenza defenses. *New England Journal of Medicine* 2005;**353**(25):2633–6.

Ou 1992

Ou M. *Chinese-English Manual of Commonly Used in Traditional Chinese Medicine*. 1. Guangdong: Guangdong Scientific and Technological Publishing House, 1992.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Journal of the American Medical Association* 1995;**273**:408–12.

Smith 2006

Smith NM, Bresee JS, Shay DK, Uyeki TM, Cox NJ, Strikas RA. Prevention and Control of Influenza -Recommendations of the Advisory Committee on Immunization Practices (ACIP). Recommendations and Reports (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5510a1.htm>) 2006.

WHO 2003

World Health Organization. Influenza. <http://www.who.int/mediacentre/factsheets/fs211/en/> (Accessed 2006) 2003.

WHO 2007

World Health Organization. WHO guidelines for investigation of human cases of avian influenza A(H5N1). http://www.who.int/csr/resources/publications/influenza/WHO_CDS_EPR_GIP_2006_4r1.pdf (Accessed 2007) 2007.

Wiselka 1994

Wiselka M. Influenza: diagnosis, management and prophylaxis. *BMJ* 1994;**308**:1341–5.

Xu 1998

Xu QP, Zhao L. *Pharmacology of Traditional Chinese Medicine*. 1st Edition. Beijing: People Health Publishing House, 1998.

Zhang 1991

Zhang EQ. *The Chinese Materia Medica*. 1st Edition. Shanghai: Publishing House of Shanghai College of Traditional Chinese Medicine, 1991.

Zhao 2001

Zhao EJ. *Pulse Diagnosis in Chinese Medicine*. 2nd Edition. Tianjin: Tianjin Scientific and Technologic Publishing House, 2001.

References to other published versions of this review**Chen 2005**

Chen XY, Wu TX, Liu GJ, Wang Q, Zheng J, Wei J, et al. Chinese medicinal herbs for influenza. *Cochrane Database of Systematic Reviews* 2005, Issue 1. [DOI: 10.1002/14651858.CD004559.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Shi 2004

Methods	Trial design: randomised controlled parallel study Randomisation procedure: random number generated by NDST statistical software Blinding: no blinding	
Participants	Country: China Setting: Hangzhou, Zhejiang province 61 children patients with type-B influenza (32 cases in therapy group, 29 cases in control group) Diagnostic criteria: (1) sudden fever; (2) accompanied with respiratory catarrh symptoms or alimentary tract symptoms such as abdominal pain, vomiting, diarrhoea. Examination of stool sample and vomitus under microscope was negative; (3) may be accompanied with headache and myalgia; (4) physical examination found diffused congestion of pharyngeal cavity or hyperplasia of lymph follicle in the pharyngeal posterior wall; (5) over 5 people who had been in touch had similar symptoms; (6) WBC count of routine blood test was normal or decreased, neutrophil cell count was normal or lymphatic cell count was high Baseline: gender, age, disease duration, and severity of disease were similar in the two groups ($P > 0.05$) Withdrawal: not reported	
Interventions	1. TCM group (trial group): E Shu You glucose injection containing 0.1 g E Shu You and 12.5 g glucose per 250 ml injection (10 mg/kg/d iv q.d.) 2. Control group: ribavirin injection (10-15 mg/kg/d) + vitamin C (50 mg/kg/d) + 10% glucose 500 ml: 10% normal saline 10 ml iv q.d. Erythromycin capsule 30 ~ 50 mg orally b.i.d. was given to both groups. Ibuprofen was given temporarily to patients with high fever Treatment duration was 3 to 5 days	
Outcomes	Recovery: temperature falls to normal within 72 hours, symptoms and physical signs had improved by more than 90% Marked improvement: temperature falls to normal within 72 hours, symptoms and physical signs had improved by more than 70% General improvement: temperature falls but not to normal within 72 hours, symptoms and physical signs had improved by more than 30% No improvement: temperature does not falls or even increased within 72 hours, symptoms and physical signs had improved by less than 30%	
Notes	Influenza virus B was isolated by CDC in Hangzhou city in this local epidemics	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Xue 1999

Methods	Trial design: randomised controlled parallel study Randomisation procedure: the allocation sequence was generated by computer software Blinding: double-blinding	
Participants	Country: China Setting: influenza epidemic area 951 healthy participants and participants with influenza were recruited in this trial (519 cases in therapy group with 124 influenza participants, M/F 316/203; 432 in control group with 89 influenza participants M/F 263/169) Data from healthy participants on entrance were used for analyses of the prevention study. Data from those with influenza on entrance and who subsequently developed influenza from the prevention study were used in the treatment analyses All the participants had similar typical influenza symptoms and disease duration within 48 hours In the treatment study: 202 participants were in the therapy group and 230 participants were in the control group Withdrawal: not reported	
Interventions	1. TCM group (trial group): Ganmao capsule (3.5 g, t.i.d, orally) 2. Control group: amantadine capsule (0.07 g, t.i.d, orally) Therapy duration was 7 days for both prevention and treatment studies	
Outcomes	Influenza morbidity within 7 days of treatment Recovery: the systemic symptoms and local typical symptoms clear within 24 h to 48 h after administration Ineffectiveness: the rest of patients other than who achieved recovery were defined as inefficacy Patients using other drugs during the study were not included in the effectiveness statistics	
Notes	Influenza virus A3 was isolated by CDC in Tianjin city in local epidemics	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

b.i.d: twice a day

CDC: Centers for Disease Control and Prevention

h: hours

t.i.d: three times a day

q.d: once a day

M/F: male/female

NDST: New Drug Statistical Treatment

TCM: Traditional Chinese Medicine

WBC: white blood cell

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

Du 1991	It was claimed to be an 'RCT'. We telephone interviewed the original author and learned that it was not an RCT
Hamazaki 2006	Outcome measures were hemagglutinin titers and natural killer (NK) activity which did not match our outcome measures regulated in this review
Hang 1998	Observation duration (3 to 5 days) exceeded the criteria of observational span specified in this review
Hou 2002	It was claimed to be an 'RCT'. We telephone interviewed the original author and learned that it was a quasi-RCT of alternative allocation
Huang 2003	A quasi-RCT. Participants were allocated according to the entry odd/even days
Jiang 2003	One TCM was compared with another TCM
Jin 1998	Complications of influenza were included in this study
Kubo 2007	The drug used was a Japanese herbal medicine
Li 2001	It was claimed to be an 'RCT'. We telephone interviewed the original author and learned that it was not an RCT
Li 2005	Participants had severe influenza with complications
Lindenmuth 2000	Participants had severe influenza with complications with the common cold and influenza were not analysed separately
Liu 2002	The participants had severe influenza with pneumonia complication - found by lab tests and chest radiographs
Lu 2004	Participants with common cold and influenza were included, and data for influenza were not separately reported
Qu 2005	It was claimed to be an 'RCT'. We telephone interviewed the original author and learned that it was a quasi-RCT. Participants were allocated according to entry odd/even day
Wang 2001	Herbal medicine were compared with chemical medicine plus another Chinese patent medicine
Xu 2001	It was claimed 'RCT'. We telephone interviewed the original author and learned that it was a quasi-RCT of alternative allocation
Yang 2000a	It was claimed 'RCT'. We telephone interviewed the original author and learned that it was a quasi-RCT of alternative allocation
Yang 2000b	Herbal medicines were compared with chemical medicines plus another Chinese patented medicine

(Continued)

Yang 2005a	One TCM was compared with another TCM
Yang 2005b	One TCM was compared with another TCM
Yao 2003	It was claimed 'RCT'. We telephone interviewed the original author and learned that it was a quasi-RCT of alternative allocation
Yu 2000	One TCM was compared with a chemical medicine plus another TCM
Yuan 2003	It was claimed 'RCT'. We telephone interviewed the original author and learned that it was not an RCT
Zeng 2004	Herbal medicines were compared with chemical medicines plus another Chinese patented medicine. The patients had complications of pneumonia, bronchitis and tonsillitis
Zhang 2000	The patients had the complication of pneumonia, found by lab tests and chest radiographs
Zhang 2002	One TCM was compared with another TCM
Zhang 2004	One TCM was compared to another TCM plus an antiviral drug
Zhang 2005	One TCM was compared with another TCM
Zhao 2006	One TCM was compared with another TCM
Zhong 2005	One herbal medicine was compared to another Chinese patented medicine

RCT: randomised controlled trial

TCM: traditional Chinese medicine

DATA AND ANALYSES

Comparison 1. Day 2 recovery rate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Herbal medicine versus antiviral drugs	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Ganmao capsule versus amantadine	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 2. Day 3 recovery rate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Herbal medicine versus antiviral drugs	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 E Shu You versus ribavirin	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 3. Day 3 marked improvement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Herbal medicine versus antiviral drugs	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 E Shu You versus ribavirin	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 4. Day 3 partial improvement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Herbal medicine versus antiviral drugs	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 E Shu You versus ribavirin	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 5. Day 3 no improvement rate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Herbal medicine versus antiviral drugs	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 E Shu You versus ribavirin	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 6. Influenza incidence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Herbal medicine versus antiviral drugs	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Ganmao capsule versus amantadine	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 7. Adverse reaction

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse reaction in the gastrointestinal tract	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Herbal medicine versus antiviral drugs	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 Day 2 recovery rate, Outcome 1 Herbal medicine versus antiviral drugs.

Review: Chinese medicinal herbs for influenza

Comparison: 1 Day 2 recovery rate

Outcome: 1 Herbal medicine versus antiviral drugs

Study or subgroup	Treatment	Control	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
	n/N	n/N		
1 Ganmao capsule versus amantadine				
Xue 1999	168/202	37/230	—	5.17 [3.82, 6.99]

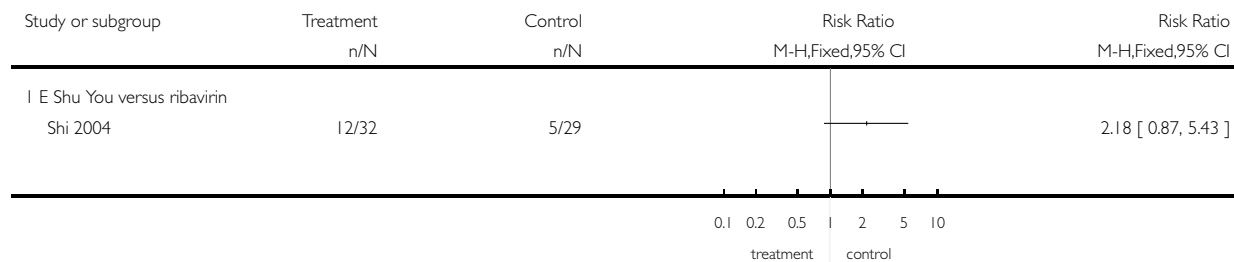
0.05 0.2 | 5 20
treatment control

Analysis 2.1. Comparison 2 Day 3 recovery rate, Outcome 1 Herbal medicine versus antiviral drugs.

Review: Chinese medicinal herbs for influenza

Comparison: 2 Day 3 recovery rate

Outcome: 1 Herbal medicine versus antiviral drugs

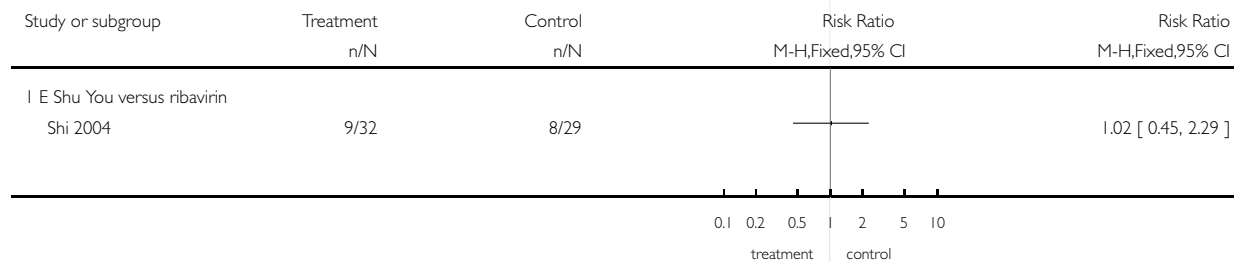


Analysis 3.1. Comparison 3 Day 3 marked improvement, Outcome 1 Herbal medicine versus antiviral drugs.

Review: Chinese medicinal herbs for influenza

Comparison: 3 Day 3 marked improvement

Outcome: 1 Herbal medicine versus antiviral drugs

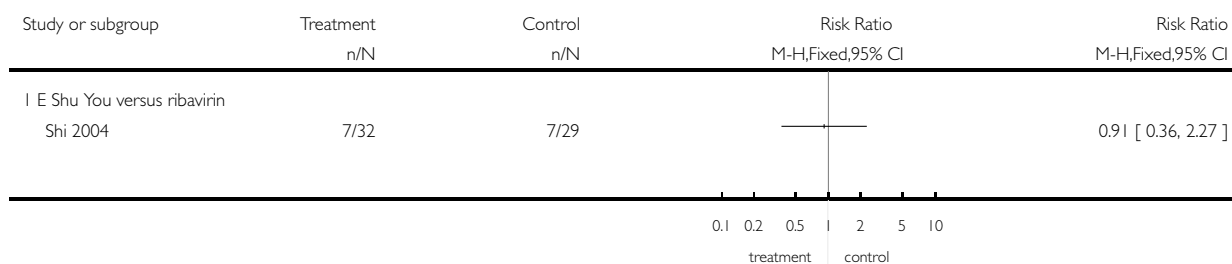


Analysis 4.1. Comparison 4 Day 3 partial improvement, Outcome 1 Herbal medicine versus antiviral drugs.

Review: Chinese medicinal herbs for influenza

Comparison: 4 Day 3 partial improvement

Outcome: 1 Herbal medicine versus antiviral drugs

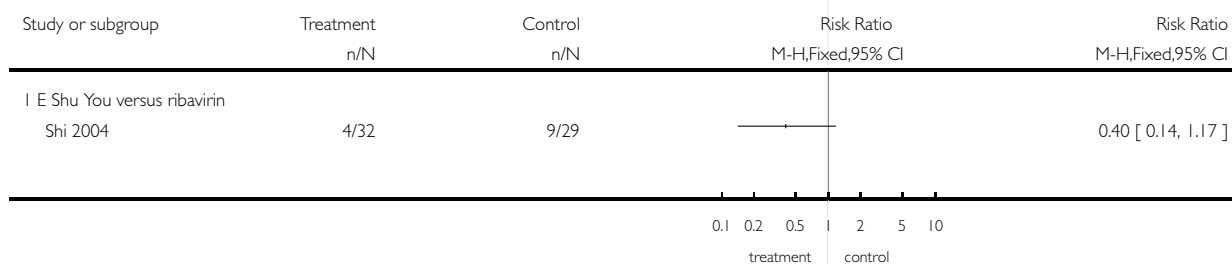


Analysis 5.1. Comparison 5 Day 3 no improvement rate, Outcome 1 Herbal medicine versus antiviral drugs.

Review: Chinese medicinal herbs for influenza

Comparison: 5 Day 3 no improvement rate

Outcome: 1 Herbal medicine versus antiviral drugs

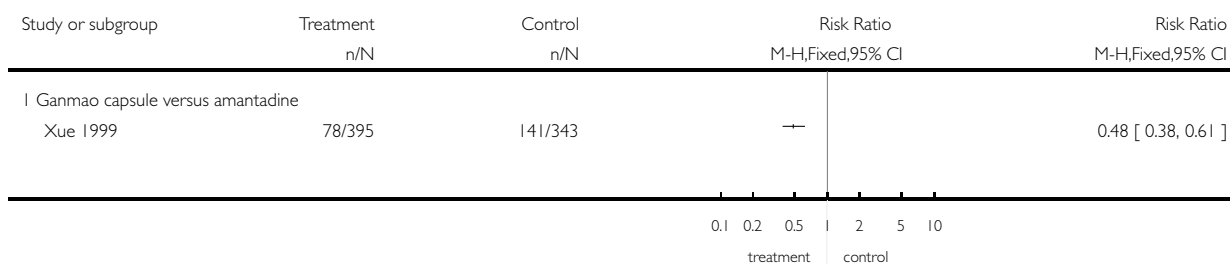


Analysis 6.1. Comparison 6 Influenza incidence, Outcome 1 Herbal medicine versus antiviral drugs.

Review: Chinese medicinal herbs for influenza

Comparison: 6 Influenza incidence

Outcome: 1 Herbal medicine versus antiviral drugs

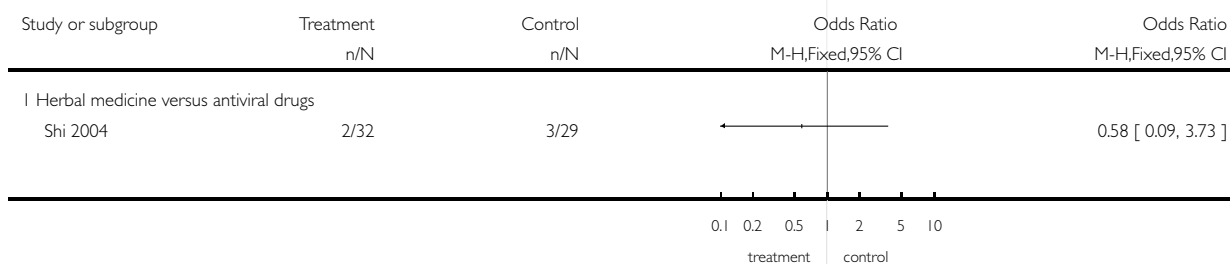


Analysis 7.1. Comparison 7 Adverse reaction, Outcome 1 Adverse reaction in the gastrointestinal tract.

Review: Chinese medicinal herbs for influenza

Comparison: 7 Adverse reaction

Outcome: 1 Adverse reaction in the gastrointestinal tract



WHAT'S NEW

Last assessed as up-to-date: 31 December 2006.

21 January 2010	Amended	Contact details updated.
-----------------	---------	--------------------------

HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 1, 2005

4 July 2008	Amended	Converted to new review format.
22 March 2007	New citation required and conclusions have changed	<p>In this 2007 updated review we added “to assess the effectiveness of Chinese medicinal herbs in preventing cases of influenza” in the Objectives section because Chinese medicinal herbs were also commonly used for preventing influenza during epidemic periods.</p> <p>We excluded quasi-RCTs. We interviewed the trial authors and excluded any supposed RCTs which we discovered were in fact not randomised controlled trials.</p> <p>We excluded the interventions of one herbal medicine compared with another herbal medicine as we were uncertain of the control herb’s efficacy.</p> <p>Accordingly, the references to studies were changed and new trials were found.</p> <p>We also changed to the types of outcome measures because we added prophylactic studies and continuous data for analyses. As a result, the Description of studies, Methodological quality of included studies, Results and Discussion section were amended.</p>
28 October 2004	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Xiaoyan Chen (XC) and Taixiang Wu (TW) were responsible for developing the protocol, searching for trials, quality assessment of the trials, data extraction, data analysis, review development and updating.

Guanjian Liu (GL) was responsible for quality assessment of the trials, data extraction and data analysis.

Jieqi Qiao (JQ), Xin Duan (XD), Juan Ni (NJ), Likun Zhou (LK), Qin Wang (QW), Jie Zheng (JZ) and Jaifu Wei (JW) were responsible for searching trials.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Chinese Cochrane Center, West China Hospital of Sichuan University, China.

External sources

- Chinese Medical Board of New York (CMB), USA.

INDEX TERMS

Medical Subject Headings (MeSH)

Amantadine [therapeutic use]; Antiviral Agents [therapeutic use]; Drugs, Chinese Herbal [adverse effects; *therapeutic use]; Influenza, Human [*drug therapy]; Phytotherapy [adverse effects; *methods]; Randomized Controlled Trials as Topic; Ribavirin [therapeutic use]

MeSH check words

Humans