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## EVIDENCE-BASED REVIEW

# Traditional Chinese medicine in the treatment of acute respiratory tract infections<sup>☆</sup>

Taixiang Wu<sup>a,\*</sup>, Xunzhe Yang<sup>a</sup>, Xiaoxi Zeng<sup>a</sup>, Phillipa Poole<sup>b</sup>

<sup>a</sup> Chinese Cochrane Centre, Chinese Evidence-Based Medicine Centre, International Clinical Epidemiology Resource and Training Center, West China Hospital, Sichuan University, No. 37, Guo Xue Xiang, Chengdu 610041, China

<sup>b</sup> Department of Medicine, University of Auckland, Private Bag 92019, Auckland, New Zealand

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### Summary

**Aims:** To review the evidence from Cochrane systematic reviews for the effectiveness of traditional Chinese medicinal (TCM) herbs for treating acute respiratory tract infections (ARTIs) and to discuss the limitations of current clinical trials of TCM.

**Findings:** Evidence from six Cochrane systematic reviews was weak owing to the lack of high-quality TCM trials. Limitations were usually due to biases that influenced the validity of results.

**Conclusions:** TCM is widely used for treating ARTIs. However, none of the identified studies has been well designed or conducted. In this overview, we suggest that clinical trials of TCM for ARTIs need to be re-run in accordance with internationally recognized standards.

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## Introduction

Acute respiratory tract infections (ARTIs) range from minor (e.g. common cold) through to very serious conditions (e.g. severe acute respiratory syndrome). ARTIs are caused by over 200 viruses or bacteria. They are transmitted directly through person-to-person contact, either by airborne

droplets from a sneeze or cough, or by direct contact with nasal or throat secretions, articles freshly soiled with secretions of the nose and throat, or by transmission via an object indirectly. For example, sore throat can either be a disease in itself, or can result from other diseases, such as influenza and glandular fever.<sup>1–4</sup>

Uncomplicated ARTIs, such as the common cold and sore throat, recover spontaneously as a result of antibodies

<sup>☆</sup> The following Cochrane reviews have been cited in this Evidence-Based Review: Del Mar CB et al. Antibiotics for sore throat, Issue 4, 2006; Wei J et al. Chinese medicinal herbs for acute bronchitis, Issue 3, 2005; Chen XY et al. Chinese medicinal herbs for influenza, Issue 1, 2005; Gu R et al. Chinese medicinal herbs for measles, Issue 2, 2006; Wu T et al. Chinese medicinal herbs for the common cold, Issue 1, 2007; Liu X et al. Chinese herbs combined with Western medicine for severe acute respiratory syndrome (SARS), Issue 1, 2006.

\* Corresponding author.

E-mail address: [txwutx@hotmail.com](mailto:txwutx@hotmail.com) (T. Wu).

produced by the patient's own immune system targeting the virus. In general, no specific antiviral treatment is used. Treatment aims to alleviate symptoms and prevent complications. Antibiotics are used for bacterial infections. However, antibiotics only have a modest effect over placebo for acute bronchitis<sup>5</sup> and sore throat.<sup>6,7</sup> For the common cold and influenza, over-the-counter decongestants, antihistamines, cough suppressants, and expectorants may be used for symptomatic relief.

Traditional Chinese Medicine (TCM) is a unique system with special aetiology and theories for treatment. TCM drug treatment typically consists of a complex prescription of a combination of components according to TCM signs. These include whether the patients themselves feel cold and chilly; experience nasal obstruction; do not sweat; generally have a high temperature with a thin, white coating on the tongue; have a productive cough; do not feel chilly; have an elevated temperature, with a thin and slightly yellow coating on the tongue; or have a productive cough. Colds are categorized as 'chills cold' or 'fever cold'. Shigao (gypsum fibrosum) is used to abate fever; Caihu (bupleurum chinenses DC) and Jinjie (herba schizonepetae) are used as analgesics; Banxia (rhizoma pinelliae) is dispensed to loosen sputum and suppress cough; Fangfeng (radix saphoshnikiviae) and Zhishuye (folium perillae) are used for 'chill cough'; Jinyinghua (flos lonicerae) and Bohe (herba menthae) for 'fever cough', and so on. Elements of a TCM formulation are meant to interact and co-ordinate with each other. These may be combined in a soap-like solution, or 'decoction' of TCM.

In this Evidence-Based Review, we aim to summarize the evidence from Cochrane systematic reviews for the effectiveness of TCM herbs in treating ARTIs, and to discuss the limitations of TCM clinical trials in the field.

## Method and findings

We conducted a comprehensive search for Cochrane reviews of TCM for ARTIs. We screened the Cochrane Database of Systematic Reviews in the Cochrane Library, Issue 3, 2007. The search string contained (traditional AND Chinese AND medicine) OR herb\*. We found 70 Cochrane reviews and protocols. After scrutiny, six reviews were identified that fulfilled the inclusion criteria. The six reviews related to the use of TCM in the treatment of acute bronchitis, influenza, measles, sore throat, common cold and severe acute respiratory syndrome (SARS), respectively.

### Chinese medicinal herbs for acute bronchitis

The initial version of this review was published in the Cochrane Database of Systematic Reviews, Issue 3, 2005.<sup>8</sup> Fourteen studies were included in the review, involving a total of 2771 participants with acute bronchitis. However, study quality (randomization, blinding and allocation concealment) was poor. Because the formulations used were heterogeneous, the outcomes were analyzed separately, and not combined. All the 14 formulations in the studies seemed to show significant benefits compared with conventional medicine. For example, TCM formulation 'Xiao'er Xiaoji Zhike Koufuye' oral decoction was more effective

than cefotaxime plus flumequidil (*N*-acetylcysteine) for resolution of cough (WMD -0.62 days, 95% CI -1.12 to -0.12), for clearance of fever (WMD -1.22 days, 95% CI -1.67 to -0.77), for reducing the duration of wheezing (WMD -0.44 days, 95% CI -0.74 to -0.14), and for resolution of rales (WMD -1.00 days, 95% CI -1.47 to -0.53).

'Yuxingcao' atomisation aerosol was more effective than gentamicin atomisation aerosol for resolution of cough (WMD -1.37 days, 95% CI -1.67 to -1.07), for clearance of fever (WMD -0.92 days, 95% CI -1.03 to -0.81), and for relief of rales (WMD 0.60 days, 95% CI 0.19-1.01).

The TCM patent medicine 'Shiwei Longdanhua Keli' oral decoction plus antibiotics was more effective than antibiotics alone for resolution of cough (WMD -2.40 days, 95% CI -2.84 to -1.96), for clearance of fever (WMD -0.99 days, 95% CI -1.44 to -0.54), and for resolution of rales (WMD -2.76 days, 95% CI -3.26 to -2.26).

The TCM formulation 'Tanreqing' injection was more effective than levofloxacin for resolution of cough (WMD -3.17 h, 95% CI -5.95 to -0.39), for clearance of fever (WMD -32.13 h, 95% CI -34.81 to -29.45), and for normalization of chest X-ray (RR 1.28, 95% CI 1.01-1.61).

The major limitation of this Cochrane review was that inclusion of the studies was dependent upon the term 'random' appearing in the text. The original trial authors have now been interviewed by telephone and no trial has been identified as a true randomized-controlled trial (RCT). This particular Cochrane review is in the process of being updated. According to knowledge gained during the summer of 2005, it is estimated that only a small number of claimed RCTs published in China are authentic RCTs.<sup>9</sup>

### Chinese medicinal herbs for influenza

The initial version of the review on Chinese medicinal herbs for influenza was published in the Cochrane Database of Systematic Reviews, Issue 1, 2005.<sup>10</sup> Eleven studies with the number of participants ranging from 52 to 479, for a total of 2088, were included. One study used a Chinese patent medicine, and the other 10 studies used TCM formulations in decoctions prepared in the respective hospitals. Two years after publication of the review, the review authors telephoned the 11 trial authors and found that only two studies were authentic RCTs. This review is in the process of being updated and will include these new findings.

Of the two authentic RCTs, 61 were children with influenza B infection and 951 were participants with influenza A3/H3N2. For children with influenza B, TCM Eshuyou oral decoction (volatile oil extracted from Zedary) had better effects but was not significantly different from ribavirin for recovery within 3 days of treatment (12/32 vs 5/29, RR 2.18, 95% CI 0.87-5.43). For participants with influenza A3/H3N2, Ganmao Capsule had significantly better effects than amantadine for recovery within 2 days of treatment (168/202 vs 37/230, RR 5.17, 95% CI 3.82-6.99).

### Chinese medicinal herbs for measles

The review on Chinese medicinal herbs for measles was published in the Cochrane Database of Systematic Reviews, Issue 2, 2006.<sup>11</sup>

Strict methods for identifying study design were used in this review. Twenty-eight studies were retrieved, which claimed to randomly allocate the participants. The authors of the 19 RCTs were interviewed by telephone. It was revealed that the allocation methods they had used were not true randomization. Three studies were excluded owing to participant complications. The remaining six study authors were unable to be contacted and will be assessed only if they demonstrate random allocation of the participants. Thus, there is currently no RCT evidence for use of TCM in measles.

## Chinese medicinal herbs for sore throat

The review on Chinese medicinal herbs for sore throat was published in the Cochrane Database of Systematic Reviews, Issue 3, 2007.<sup>12</sup>

Strict methods for identifying RCTs were used in this review. The authors of the 54 RCTs were interviewed; only seven trials involving 1253 participants were identified as using authentic randomization techniques, but otherwise had poor methodological quality raising the possibility of selection bias or detection bias, or both. Conflict of interest may have been another factor in producing a positive result in three studies as the prepared drugs were made in the respective hospitals.

Three TCM formulations were shown to be superior to the control drug in improving recovery: Ertong Qingyan Jiere Koufuye oral decoction was more effective than Fufang Shuanghua Koufuye decoction for acute pharyngitis (OR 1.54, 95% CI 1.11–5.74). Yanhouling decoction was more effective than the gentamicin atomised inhalation aerosol, a non-standard treatment, for acute pharyngitis (OR 5.39, 95% CI 2.69–10.81). Qinganlan Liyan Hanpian tablet was more effective than the Fufang Caoshanhu Hanpian tablet for chronic pharyngitis (OR 2.25, 95% CI 1.08–4.67), and four formulations were shown to be equal in efficacy to the control.

## Chinese medicinal herbs for the common cold

The review of Chinese medicinal herbs for the common cold was published in the Cochrane Database of Systematic Reviews, Issue 1, 2007.<sup>13</sup>

The strict procedure of interviewing the original trial authors of claimed 'RCTs', to guarantee the validity of the allocation method used for included studies was also conducted in this review.

A total of 348 trials claiming to be randomized were retrieved. The authors of 295 trials were contacted by telephone. Of these studies, 234 were excluded either because the trial authors misunderstood the concept of randomization or the trials were multiple printings of same study. One hundred studies were relegated to the 'awaiting assessment' section because the trial authors could not be contacted, or refused to be interviewed. Fourteen studies were identified as true RCTs and were included for assessment.

Of the 14 studies, two tested the same preparation against the same TCM formulation control. The other 12 studies tested different preparations for patients with

different types of TCM signs (zheng xing). Therefore, the data were assessed separately.

Five studies of herbal preparations reported a statistically significantly shorter duration of symptoms after treatment with the intervention compared with the control. Of the five studies, three were for children with 'fever cold' (Fengre zheng).

Qinwen Keli oral decoction was more effective than Kangbingdu Koufuye oral decoction (RR 2.19, 95% CI 1.61–2.96); Shuanghua Penwuji aerosol was more effective than Shuanghuanglian Qiwuji aerosol (RR 1.48, 95% CI 1.11–1.79); and TCM cream was more effective than penicillin (RR 2.10, 95% CI 1.20–3.67).

In one trial conducted for adults with 'chills cold' (Fenghan zheng), Sufeng Ganmao Koufuye oral decoction was more effective than Ganmao Qinre Koufuye oral decoction (RR 1.43, 95% CI 1.02–1.99); in one trial in 'fever cold' (Fengre zheng), Qinkailing injection was more effective than lincomycine given in three doses, in the treatment of adults with the common cold (120 ml/day RR 1.41, 95% CI 1.07–1.86; 160 ml/day RR 1.41, 95% CI 1.08–1.86, and 200 ml RR .52, 95% CI 1.15–2.00).

Seven studies testing six TCM preparations showed no statistically significant difference compared with controls in duration of symptoms. These included pooled analyses of two studies of Sanhan Jiere Koufuye oral decoction compared with Fenghan Biaoshi Ganmao Chongji oral decoction (combined RR 1.51, 95% CI 0.79–2.90) for adults with 'chills cold' (Fenghan zheng); Jinlian Qinre capsule compared with Jinlian Qinre Keli oral decoction (RR 0.97, 95% CI 0.58–1.62) for adults with 'fever cold' (Fengre zheng); Gegen Cenlianweiwan tablet compared with Yinqiao Jiedupian tablet (RR 1.17, 95% CI 0.80–1.73) for children with fever cold (Fengre zheng); Jianer Qinjiye oral decoction compared with Qinre Jiedu Koufuye oral decoction (RR 1.45, 95% CI 0.99–2.13) for children who had not been categorized according to TCM signs; Huanghu Jiere Daipaoji oral decoction compared with Shiqi Ganmao Daipaoji oral decoction (RR 3.62, 95% CI 0.88–14.91) for children with 'fever cold'; Caichen Qinre Weixin Guanchongji oral decoction with virazole and acetaminophen (RR 1.33, 95% CI 0.68–2.62) for children with 'fever cold' (Fengre zheng) and others with 'chills cold' (Fenghan zheng).

## Chinese herbs combined with Western medicine for severe acute respiratory syndrome

The review of Chinese herbs combined with Western medicine for SARS was published in the Cochrane Database of Systematic Reviews, Issue 1, 2006.<sup>14</sup>

An important question arose from the SARS outbreak in 2003: "Why was the case-fatality rate lower in mainland China (7%, 349/5327) than in both Hong Kong (17%, 299/1755) and Taiwan (11%, 37/346)?" The mortality level in mainland China was also lower than that in the rest of the world (9.6%, 774/8096).<sup>15,16</sup> During the early stage of the SARS outbreak, Western medicine, specifically corticosteroids, was combined with Chinese herbal medicines in an effort to promote non-specific immunity to combat inflammation. The State Administration of Traditional Chinese Medicine, the Chinese

Ministry of Health General Office, issued a rule of combining Western and Chinese herbal medicine (ICWM) for this rapidly spreading disease. SARS was classified as a plague that needed to be treated in accordance with the 'wei, qi, ying, xue and sanjiao bianzheng lunzhi' theory. In keeping with this theory, some herbal medicinal extract injections to clear fever (qin re), remove dampness (qu shi), relieve asthma (zhi chuan), promote and regulate immunologic function (fu zheng), resist viruses and remove toxins (jie du), were recommended for clinical use.<sup>17</sup>

The Cochrane systematic review, conducted by Liu et al.<sup>14</sup> included 12 RCTs, and one quasi-RCT had a total of 654 participants using 12 different TCM formulations. They carried out a combined analysis of two trials using the same TCM formulation plus Western medicine, and separately analyzed four studies using different formulations plus Western medicine vs Western medicine alone to compare mortality between the two therapies. TCM did not show any benefit in reducing mortality compared with Western medicine alone (RR 0.31, 95% CI 0.07–1.38, RR 0.27, 95% CI 0.01–6.11; RR 0.41, 95% CI 0.04–4.78; RR 0.30, 95% CI 0.01–7.70; and RR 0.19, 95% CI 0.01–4.06, respectively). Whether or not TCMs can decrease mortality from SARS remains an unanswered question (Table 1).

## Discussion

It is encouraging that clinical trials of TCM in ARTIs have been conducted; however, to date these have in common a weak study design, leading to potential biases in evaluating the effectiveness of the intervention.

Approaches for minimizing bias such as the use of strict protocols, randomization, concealment of allocation, and double-blinding were underused in these trials. The

reporting of TCM trials is usually cursory, with a lack of description surrounding important detailed information, such as how the allocation sequence was generated; recruitment and enrolment of the participants; blinding for assessors and analyzers, statistical methods and number of drop-outs. A large number of the trials claimed to be RCTs; however, most of the trial authors misunderstood the concept of randomization allocation. In the reviews in which the reviewers subsequently contacted the authors, the percentage of authentic RCTs was 6.7% (23/342). This highlights the need for reviewers, including those doing Cochrane reviews, to use a strict method to identify whether the trial authors used the correct method to allocate participants when conducting a systematic review, and not just relying on published reports. It also emphasizes the importance of using a quality scoring system, and planning, *a priori*, subgroup analysis of trials based on study quality. Results from larger, better-quality trials are less likely to be affected by bias and thus more likely to be valid.

Many trials tested self-prepared formulations of the trial authors or their colleagues, or the decoctions were manufactured by their hospitals or patients themselves. As the trialists were involved in the design of the formulations and conducted the trials, this may have biased investigators in favour of the intervention.

Few studies used a placebo as a control. Instead 'positive effect drugs' were used. Most Chinese trialists select the control drugs by a rule of 'the effect was commonly acknowledged'. This rule may lead to conflict of interest bias, and subjective over- or under-estimate of the effect of the trial preparation depending on the aim of the study. If a preparation was tested as the intervention, it had a high rate of effectiveness; if used as a control drug by another author, it may have had a much lower rate of

**Table 1** Cochrane reviews of traditional Chinese medicine for severe acute respiratory syndrome

Condition	Number of trials included	Main results
Acute bronchitis	14 in the original version, but no study identified as an authentic RCT	No evidence from RCTs yet
Influenza	11 in original review, only two will be included in updated version	One poor-quality trial showed that TCM may decrease influenza symptoms and speed up recovery. Overall methodological quality poor. No evidence from RCTs yet
Measles	No authentic trial was identified for inclusion.	
Sore throat	Seven trials identified and included	Three formulations were shown to be superior to the control formulation in improving recovery. All trials were of methodologically poor quality.
Common cold	14 trials identified and included	In five studies, treatment with herbal preparations resulted in a statistically significantly shorter duration of symptoms compared with control.
SARS	13 studies included	TCM did not show any benefit in reducing mortality compared with Western medicine alone.

RCTs, randomized-controlled trials; SARS, severe acute respiratory syndrome; TCM, traditional Chinese medicine.

effectiveness. Therefore, it is difficult to determine the efficacy of the intervention drug. Where the intervention drug was equal in efficacy to the control drug, no conclusion could be made.

Sample sizes were not reported in most of the TCM studies, which makes it difficult to assess if observed differences between the two groups were statistically or clinically important, or if trials were underpowered. Some studies used unequal arms in their design, with some having a small number of participants in their control group. This would contribute to selection bias.

The traditional use of TCM is in contrast to the pharmacological agents used in Western medicines, for which the chemical constituents, their quantities, and the percentage of any impurities of contaminants are known precisely. In addition, the variation between different production batches of Western medicinal drugs is kept within specified limits. In contrast, variation between formulations and batches of pharmacological agents is inevitable in TCM, although 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 TCM components used in the trials were not adequately described. The variability in individual components of herbal preparations and the variability between different preparations of combination products meant that any meaningful scientific evaluation is difficult to make without precise descriptions of the components of TCM formulations for the decision makers' consideration. Because of the variability, use of Chinese names alone for herbal preparations is not sufficient. In addition to folk or specific TCM names, each preparation should be described, giving the internationally recognized taxonomic names (Genus species) of all plants included, the plant organ, along with proportions.

TCM has an overall treatment concept that differs from Western medicine. When using a TCM preparation for treating a disease, the type of 'zheng', the TCM signs, of a disease has to be matched. But some studies did not state whether the TCM control drug matched the type of 'zheng' or not. If the control drug does not match the 'zheng', the interpretation of results should refer to a placebo. Unmatched formulations may be detrimental to the patient. It was often necessary to include TCM signs as a secondary or an additional outcome in the trials. However, it is difficult to compare or quantify TCM signs as most of them are subjective or non-specific outcomes. For example, 'mai xiang' means pulse presentations. Diagnosing 'mai xiang' in TCM is a complex technique, dependent upon the TCM physician's feelings and experience. The descriptors 'marked improvement' and 'improvement' are commonly used to assess the change in TCM signs. These are based on the participants' feelings and assessor's subjective judgment. There seems a need for TCM researchers and physicians to develop an accurate, repeatable, and simple set of TCM measures to use as outcomes in clinical trials.

Along with the Cochrane review on Chinese herbs combined with Western medicine for SARS,<sup>17</sup> there have been two other reviews published addressing the question as to whether TCM lowers case-fatality rates in SARS or not. The first of these pooled results for five different

TCM formulations in five studies, finding a statistically significant, lower mortality in TCM plus conventional medicine groups than in conventional medicine groups alone (RR 0.32, 95% CI 0.12–0.91).<sup>18</sup>

In the other review<sup>19</sup> pooled data from four studies showed a statistically significant lower mortality in TCM plus conventional medicine than in conventional medicine alone (OR 0.32, 95% CI 0.14–0.71), but a sensitivity analysis that excluded an unbalanced two-arm study in which the number of severely ill patients was higher in the conventional medicine group than the TCM group (19 vs 13) found that there was no statistical difference between the two groups (OR 0.53, 95% CI 0.20–1.41). The difference in mortality between the two therapies may, therefore, have been due to selection bias.

The interpretations in these two reviews by Liu et al.<sup>18</sup> and Wu et al.<sup>19</sup> were similar to that of the Cochrane review in that TCM therapy may contribute to a decrease in mortality from SARS. However, because of poor methodological quality of the included studies, the evidence was weak and an affirmative conclusion cannot be drawn.

The TCM effects on secondary outcomes such as symptoms, lung infiltrate absorption, dosage of corticosteroids, quality of life of SARS patients, and shortening the length of stay in hospital were similar in the three reviews.<sup>14,18,19</sup> This is likely because the data for calculating the results in the three reviews were extracted from different versions of the same studies. However, the number of studies included in the three reviews and the number of participants were different. Because of the issues with study quality, and the fact that these are secondary outcomes, it is difficult to draw any conclusions from the results.

The limitations of the included studies in the SARS reviews were similar to other studies. These included a lack of randomization description; unconcealed allocation sequence, and non-blinding. The shortcomings were obvious in most of the studies, with unbalanced arms suggested by different numbers of male and female participants. It is also reasonable to construe that it was difficult for physicians to mount and conduct rigorous RCTs during an outbreak of SARS. Thus, the methodological issues in these trials may be a more extreme representation of the problems seen in the conduct of TCM trials generally. The SARS outbreak was a rare opportunity to demonstrate the value of TCM. Unfortunately, as the evidence was derived from poorly designed studies, it remains unanswered whether the use of TCM saved SARS patients or not.

Such studies pose other considerations. As there is such a wide belief in the effectiveness of TCM in the treatment of diseases, particularly those that are not effectively treated by conventional medicine, the possibility of randomization to inactive placebo may not be acceptable to participants. Another challenge will be to find acceptable 'gold standard' treatments to compare with TCM formulations.

## Conclusion

At this stage, as evidence for TCM comes from poorly designed studies, no conclusions can be drawn about the effectiveness of TCM in a range of ARTIs. We would appeal, therefore, for future clinical trials of the effects of TCMs to

be conducted according to internationally acceptable standards. The Consolidated Standards for Reporting Trials of Traditional Chinese Medicine, (CONSORT for TCM) published in 2007,<sup>20</sup> should assist in the design of better-quality trials.

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