

# Traditional Chinese medicine for treating novel coronavirus (2019-nCoV) pneumonia: protocol for a systematic review and meta-analysis

CURRENT STATUS: UNDER REVISION

 Systematic Reviews  BMC

Yuxi Li  
Chengdu University of Traditional Chinese Medicine

Xiaobo Liu  
Chengdu University of Traditional Chinese Medicine

Liuxue Guo  
Chengdu University of Traditional Chinese Medicine

Juan Li  
Chengdu University of Traditional Chinese Medicine

Dongling Zhong  
Chengdu University of Traditional Chinese Medicine

Yonggang Zhang  
Sichuan University West China Hospital

Mike Clarke  
Queen's University Belfast

 [m.clarke@qub.ac.uk](mailto:m.clarke@qub.ac.uk) *Corresponding Author*  
ORCID: 0000-0002-2926-7257

Rongjiang Jin  
Chengdu University of Traditional Chinese Medicine

DOI:

10.21203/rs.2.23447/v1

SUBJECT AREAS

*Virology Infectious Diseases*

KEYWORDS

*2019-nCoV, coronavirus, pneumonia, traditional Chinese medicine, emerging infectious diseases, systematic review, meta-analysis*

## Abstract

**Background:** A new type of coronavirus, 2019 novel coronavirus (2019-nCoV), is causing an increasing number of cases of pneumonia and has been declared a Public Health Emergency of International Concern by the World Health Organization on 30 January 2020. The virus first appeared in Wuhan, China in late December 2019 and traditional Chinese medicine (TCM) is being used for its treatment. This systematic review and meta-analysis will assess studies of the effects of TCM in 2019-nCoV-infected pneumonia (NCIP).

**Methods:** We will search electronic databases including PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP) and Wanfang database using keywords related to NCIP and TCM. Reference lists of relevant trials and reviews will be searched. We will manually search grey literature, such as conference proceedings and academic degree dissertations, and trial registries. Two independent reviewers will screen studies, extract data and evaluate risk of bias. Data analysis will be conducted using Review Manager software (version 5.3.5) and R software (version 3.6.1).

**Discussion:** This study will provide a high-quality synthesis of the effects of TCM for NCIP. The use of TCM for treatment or prevention of these novel viral infections affecting the respiratory tract will be investigated.

Systematic review registration: PROSPERO registration number: CRD42020168004

## Background

Recently, a new type of coronavirus was identified and named 2019 novel coronavirus (2019-nCoV) by the World Health Organization (WHO),[1] which has been causing an increasing rate of pneumonia cases since late December 2019.[2-4] Infections were first

identified in Wuhan, China, before being detected in other Chinese cities and in more than a dozen countries around the world by early February 2020.[5] The outbreak was declared a Public Health Emergency of International Concern by the WHO on 30 January 2020. The 2019-nCoV-infected pneumonia (NCIP) is characterized by flu-like symptoms including fever, cough, severe acute respiratory distress syndrome, and in some cases death.[6-8] Human-to-human transmission has been confirmed for the virus,[9-11] which is considered related to severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). Like SARS-CoV and MERS-CoV, the 2019-nCoV is a serious threat to human health.[7, 12] As of 6 February 2020, nearly 30,000 people have been diagnosed with NCIP in the world.[13] Effective prevention and treatment are crucial in this situation. Traditional Chinese medicine (TCM) therapy is a mixture of Chinese herbs prescribed by Chinese herbalists depending on the differentiation of the patient's syndrome according to Chinese diagnostic patterns (inspection, listening, smelling, inquiry and palpation). Studies have reported that Chinese herbal formula, such as San Wu Huangqin Decoction, Lianhuaqingwen Capsule and Yinhuapinggan granule, possess antiviral effects, which might be associated with blocking of the proliferation and replication of the viral particles, and that they might be able to improve lung damage by influenza viruses.[14-16] During the SARS epidemics, TCM treatments were reported to have successfully prevented and treated SARS.[17-19] Furthermore, TCM combined with western medicine treatment regimen reduced adverse events and other complications induced by glucocorticoid, antibiotic and antiviral treatments.[20, 21]

After the pneumonia outbreak of the 2019-nCoV, the State Administration of Traditional Chinese Medicine in China led an expert team to formulate a TCM treatment Program. On 24 January 2020, the first case of a cured patient in Beijing being discharged from hospital after treatment of TCM with symptomatic therapy was reported.[22] Later, another cured

patient was reported following TCM therapy, prompting the wider application of TCM for patients with 2019-nCoV pneumonia.[23] On 27 January 2020, the General Office of the National Health and Health Commission of China and the Office of the State Administration of Traditional Chinese Medicine issued "Pneumonitis Diagnosis and Treatment Program for New Coronavirus Infection (Trial Version 4)", which included the updated TCM treatment Program, and required local health and health committees to implement and strengthen the integration of TCM and western medicine.[24]

Although TCM treatment is being applied for 2019-nCoV pneumonia, uncertainty remains about its effectiveness. Therefore, we intend to systematically review studies of TCM application in NCIP patients in order to examine the empirical evidence of the effects of TCM for 2019-nCoV pneumonia. We aim to provide a robust evidence for improvement of clinical practice in treating 2019-nCoV pneumonia.

## Methods/design

### **Study registration**

This systematic review was registered on PROSPERO (CRD42020168004) on 5 February 2020. We have prepared this protocol in accordance with the Preferred Reporting Item for Systematic Review and Meta-analysis (PRISMA-P) statement (Additional file 1).[25]

### **Inclusion criteria**

#### Type of studies

Randomized trials and quasi-randomized or prospective controlled clinical trials that have tested TCM with or without western medicine for NCIP will be included. There will be no restrictions for blinding, follow-up or publication status. Publications in English and Chinese will be included.

#### Type of participant

Patients diagnosed with pneumonia caused by 2019-nCoV without immediately life-

threatening co-morbidities will be included. There will be no restrictions with respect to gender, age or ethnicity.

#### Type of interventions

Traditional Chinese herbal medicine involving extracts from herbs, single or mixture herbal formulas regardless of their compositions or forms. TCM combined with one or more other pharmacological intervention will also be included. There will be no restrictions with respect to dosage, frequency or duration of treatment.

#### Type of comparators

There will be no restrictions with respect to the type of comparator. The comparators are likely to include western medical therapies, supportive care and other therapeutic methods.

#### Type of outcome measurements

Our primary outcomes will be survival at the end of treatment and at the end of follow-up, and time and rate of the patient becoming negative for the coronavirus. We will also assess the following outcomes at the end of treatment and at the end of follow up: days to absence of fever; symptom score (based on fever, fatigue, cough, difficulty in breathing, poor appetite, etc.); duration of each symptom; pulmonary function; inflammation index; results of chest CT; length of stay in hospital; use (including dosage and duration) of corticosteroid; quality of life; and adverse events. If other outcomes are reported in the eligible studies, these will be extracted and reported but we will give particular attention to the possibility of selective reporting bias when using any such outcomes in our review.

#### **Exclusion criteria**

(1) Suspected or misdiagnosed NCIP patients; (2) Patients with severe basic diseases that are likely to lead to death within the trial follow-up period; (3) Duplicated data or data that cannot be extracted; (4) Full text cannot be obtained.

## **Databases and search strategy**

We will search electronic databases including PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP), and Wanfang database (Wanfang Data) using keywords related to novel coronavirus, NCIP and TCM. The full search strategy for PubMed is provided in Additional file 2 and similar strategies will be applied to the other electronic databases. Reference lists of relevant trials and reviews will be searched. We will manually search grey literature such as conference proceedings and academic degree dissertations, and trial registries (both through the WHO International Clinical Trials Registry Platform (ICRP) and on the websites of national registries).

## **Study selection**

After removing duplicates, the retrieved records will be checked independently by two reviewers (XL and DZ), who will apply the eligibility criteria based on the title and abstract. Where a study is potentially eligible, the full-text will be obtained and checked independently by two reviewers (XL and DZ) to identify the eligible studies. Any disagreements will be discussed and resolved in discussion with a third reviewer (JL).

## **Data extraction**

Two independent reviewers (YL and LG) will extract data with a predefined extraction template, which includes the following items: (1) General information: first author, title, journal, year of publication, country, funding source, study design, etc. (2) Characteristics of patients: age, gender, stage and severity of disease, comorbidity, etc. (3) Characteristics of intervention: protocol of Chinese herbal medicine (types, dosage, frequency, duration etc.), protocol of comparators (types, dosage, frequency, duration etc.). (4) Characteristics of trial: sample size (numbers recruited, randomized or allocated

to the interventions by another method, followed up and analyzed), generation of randomization sequence, allocation concealment, blinding, etc. (5) Outcomes: all outcomes, main conclusions, adverse events, etc. The original authors will be contacted to request missing data where necessary. Extracted information will be cross checked. Any disagreements will be discussed and resolved in discussion with a third reviewer (YZ).

### **Assessment of risk of bias**

Two independent reviewers (YL and DZ) will assess the risk of bias of the included studies. We will follow the guidance in the latest version of *Cochrane Handbook for systematic reviews of interventions* when choosing and using tools to assessing risk of bias for randomized and on-randomized trials. Any disagreements will be discussed and resolved in discussion with a third reviewer (RJ).

### **Data analysis**

Statistical analyses will be conducted using RevMan software (version 5.3.5) and R software (version 3.6.1). If possible, analyses for all outcomes will be done by intention-to-treat. We will perform analyses to provide effect estimates for dichotomous data and continuous data, with 95% confidence intervals. We will use risk ratios (RR) for dichotomous data and mean differences (MD) for continuous data. If subsets of included studies are sufficiently homogeneous, we will perform meta-analysis for all outcomes. Heterogeneity will be detected by using a standard Chi-square test with a significance level of  $P < 0.10$ . The  $I^2$  statistic will be applied to quantify inconsistency across studies and to assess the impact of heterogeneity on the meta-analyses. Fixed-effects model will be used if there is small statistical heterogeneity among studies ( $I^2 < 50\%$ ,  $P > 0.10$ ). Otherwise, random-effects model will be used.

### **Subgroup analysis**

If an adequate number of studies are identified, we will perform subgroup analysis for the following variables: age; patients with or without other diseases; and NCIP stage at which the TCM was given.

We will also consider analyses for other subgroups as reported in the included studies, but we will give particular attention to the possibility of selective reporting bias when using any such subgroups in our review.

### **Sensitivity analysis**

To check the robustness of pooled outcome results, we will carry out sensitivity analysis to explore the influence of studies with high risk of bias.

### **Publication bias**

We will test for publication bias using the funnel plot or other corrective analytical methods, depending on the number of clinical trials included in our review.

### **Quality of evidence**

Two independent reviewers (DLZ and JL) will assess the quality of evidence for each outcome with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[26] Each outcome will be assessed for each of the five aspects: limitations, inconsistency, indirectness, imprecision, and publication bias. They will be rated as high, moderate, low, or very low level quality.

## **Discussion**

Like the outbreaks caused by SARS and MERS, the recent outbreak of 2019-nCoV in China is creating a substantial public health challenge. In 2002, TCM played an important role in the treatment of SARS, and 58.3% of confirmed cases received TCM.[27] A Cochrane Review[28] found that Chinese herbs combined with western medicine significantly improved symptoms of SARS, including decreasing body temperature, cough and breathing difficulties, dosages of corticosteroids, improving absorption of pulmonary infiltration and

quality of life. A review[29] of 90 studies of TCM for SARS revealed positive but inconclusive results about the efficacy of combined treatment, using TCM as an adjuvant. Based on previous experience of treating SARS with TCM, the General Office of the National Health and Health Commission of China and the Office of the State Administration of Traditional Chinese Medicine encouraged the integration of TCM and western medicine. Different prescriptions are recommended in different stages of disease. This is the first systematic review to examine empirical evidence of the application of TCM for 2019-nCoV pneumonia. It will provide an overview of the application of TCM in treating NCIP patients and assess the strengths and limitations of available evidence. Furthermore, we will conduct our study based on PRISMA statement and AMSTAR2 checklist to achieve as high a level of quality as possible in reporting and methodology. This review will help explore the potential role for TCM in the treatment or prevention of viral infections affecting the respiratory tract.

## Abbreviations

TCM: traditional Chinese medicine; SARS: severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; CENTRAL: Cochrane Central Register of Controlled Trials; CBM: Chinese Biomedical Literature Database; CNKI: China National Knowledge Infrastructure; VIP: Chinese Science and Technology Periodical Database; PROSPERO: Prospective Register of Systematic Reviews; NCIP: 2019-nCoV-infected pneumonia.

## Declarations

### **Ethics approval and consent to participate**

No ethics approval is required for this systematic review and meta-analysis because we will be using information from published studies. Our findings will be published in a peer-reviewed journal according to the PRISMA guidelines.

## **Consent for publication**

Not applicable.

## **Availability of data and materials**

Not applicable.

## **Competing interests**

The authors declare that they have no competing interests.

## **Funding**

This work was supported by the Education Foundation of Chengdu University of Traditional Chinese Medicine.

## **Authors' contributions**

Rongjiang Jin and Yonggang Zhang, Juan Li designed the study. Yuxi Li, Xiaobo Liu, Liuxue Guo, Juan Li, Dongling Zhong and Mike Clarke drafted the manuscript.

All authors approved the manuscript

## **Acknowledgements**

Not applicable.

## **References**

1. **Novel Coronavirus (2019-nCoV) SITUATION REPORT-1**  
[[https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019-ncov.pdf?sfvrsn=20a99c10\\_4](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019-ncov.pdf?sfvrsn=20a99c10_4)]
2. The 2019-nCoV Outbreak Joint Field Epidemiology Investigation Team, Qun Li: **An Outbreak of NCIP (2019-nCoV) Infection in China — Wuhan, Hubei Province, 2019–2020**. *China CDC Weekly* 2020, **2**(5):79-80.
3. Wenjie T, Xiang Z, Xuejun M, Wenling W, Peihua N, Wenbo X, George FG, Guizhen W: **A Novel Coronavirus Genome Identified in a Cluster of Pneumonia Cases — Wuhan, China 2019–2020**. *China CDC Weekly* 2020, **2**(4):61-62.

4. Tan WJ ZX, Ma XJ, : **A novel coronavirus genome identified in a cluster of pneumonia cases-Wuhan, China 2019-2020.** *China CDC Weekly* 2020, **2**:61-62.
5. Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E: **A Novel Coronavirus Emerging in China—Key Questions for Impact Assessment.** *New England Journal of Medicine* 2020.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X *et al*: **Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.** *Lancet* 2020:S0140-6736(0120)30183-30185.
7. Editorials: **Stop the Wuhan coronavirus.** *nature* 2020, **557**.
8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y *et al*: **Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study.** *Lancet* 2020.
9. Nishiura H, Jung S-m, Linton NM, Kinoshita R, Yang Y, Hayashi K, Kobayashi T, Yuan B, Akhmetzhanov AR: **The extent of transmission of novel coronavirus in Wuhan, China, 2020.** *J Clin Med* 2020, **9**(330).
10. Wu P, Hao X, Lau EHY, Wong JY, Leung KSM, Wu JT, Cowling BJ, Leung GM: **Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020.** *Euro Surveill* 2020, **25**(3):10.2807/1560-7917.ES.2020.2825.2803.2000044.
11. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, Xing F, Liu J, Yip CC-Y, Poon RW-S *et al*: **A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster.** *Lancet* 2020:S0140-6736(0120)30154-30159.
12. Lippi G, Plebani M: **The novel coronavirus (2019-nCoV) outbreak: think the unthinkable and be prepared to face the challenge.** *Diagnosis.*

13. **Novel Coronavirus(2019-nCoV) Situation Report-11**  
[[https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200131-sitrep-11-ncov.pdf?sfvrsn=de7c0f7\\_4](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200131-sitrep-11-ncov.pdf?sfvrsn=de7c0f7_4)]
14. Ma Q, Yu Q, Xing X, Liu S, Shi C, Luo J: **San Wu Huangqin Decoction, a Chinese Herbal Formula, Inhibits Influenza a/PR/8/34 (H1N1) Virus Infection In Vitro and In Vivo.** *Viruses* 2018, **10**(3):117.
15. Ding Y, Zeng L, Li R, Chen Q, Zhou B, Chen Q, Cheng P, Wang Y, Zheng J, Yang Z: **The Chinese prescription lianhuaqingwen capsule exerts anti-influenza activity through the inhibition of viral propagation and impacts immune function.** *Bmc Complementary & Alternative Medicine*, **17**(1):130.
16. Du H, Zhou H, Wan H, Yang J, Lu Y, He Y, Wan H: **Antiviral effects and mechanisms of Yinhuapinggan granule against H1N1 influenza virus infection in RAW264.7 cells.** *Inflammopharmacology* 2018, **26**(6):1455-1467.
17. Liu D, Liang B, Huang L, Fang Y, Zheng J, Wang G, Zhang S, Lin W, Huang T, Cai Q: **Clinical observation on the preventive effect of kangdu bufei decoction on acute severe respiratory syndrome.** *Chinese Journal of Integrated Traditional and Western Medicine* 2004, **24**(685-688).
18. Tong X, Li A, Zhang Z, Duan J, Chen X, Hua C, Zhao D, Xu Y, Shi X, Li P: **TCM treatment of infectious atypical pneumonia--a report of 16 cases.** *Journal of traditional Chinese medicine* 2004, **24**(4):266-269
19. Liu B, He L, Liang Z, Tong X, Hu J, Ni Q, Liu X, Jiao Q, Xie Y, Li P: **Effect of Chinese Herbal Medicine on Adrenal Glucocorticoids in SARS.** *China Journal of Chinese Materia Medica* 2005, **30**(23):1874-1877.
20. Hai X: **Clinical experience of SARS treatment in Guangdong province.** *Tianjin Journal of Traditional Chinese* 2003, **20**(3):24-25.

21. Jia J: **Traditional Chinese Medicine integrated western medicine for SARS.**  
*Tianjin Journal of Traditional Chinese* 2003, **20**(3):28-30.
22. **A patient diagnosed with 2019-nCoV pneumonia was discharged from Beijing**  
[[http://wjw.beijing.gov.cn/wjwh/ztzl/xxgzbd/202001/t20200124\\_1621276.html](http://wjw.beijing.gov.cn/wjwh/ztzl/xxgzbd/202001/t20200124_1621276.html)]
23. **One patient with 2019-nCoV pneumonia was discharged today in Beijing, with a total of two discharged**  
[[http://wjw.beijing.gov.cn/xwzx\\_20031/wnxw/202001/t20200125\\_1621329.html](http://wjw.beijing.gov.cn/xwzx_20031/wnxw/202001/t20200125_1621329.html)]
24. **Pneumonitis Diagnosis and Treatment Program for New Coronavirus Infection (Trial Version 4).** In. Edited by The General Office of the National Health and Health Commission of China, Office of the State Administration of Traditional Chinese Medicine. Beijing; 2020.
25. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA: **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation.** *BMJ* 2015, **349**(1):g7647-g7647.
26. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D *et al*: **Grading quality of evidence and strength of recommendations.** *BMJ (Clinical research ed)* 2004, **328**(7454):1490.
27. **The opening lecture of Symposium on treating SARS by Traditional Chinese Medicine. Symposium on treating SARS by Traditional Chinese Medicine.** In. Edited by China BSAoTCMPsRo; 2003.
28. Liu X, Zhang M, He L, Li Y: **Chinese herbs combined with Western medicine for severe acute respiratory syndrome (SARS).** *Cochrane Database Syst Rev* 2012, **10**:CD004882.
29. Leung PC: **The Efficacy of Chinese Medicine for SARS: A Review of Chinese**

**Publications After the Crisis.** *Am J Chin Med* 2007, **35**(4):575-581.

## Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

[TCM for coronavirus Additional file 1 \(PRISMA P checklist\).docx](#)

[TCM for coronavirus Additional file 2 \(PubMed\).docx](#)