



## Opinion

# Clinical practice guideline on treating influenza in adult patients with Chinese patent medicines



Lei Wu<sup>a,b,1</sup>, Yaolong Chen<sup>c,d,e,1</sup>, Yanfang Ma<sup>c,d,e</sup>, Zifeng Yang<sup>g,h,i,j</sup>, Nan Yang<sup>c,d,e</sup>, Wenzhe Deng<sup>a</sup>, Yuanbin Chen<sup>a,b</sup>, Yuanyuan Sun<sup>f</sup>, Yimin Li<sup>g,h,i,j,\*</sup>, Lin Lin<sup>a,b,\*</sup>

<sup>a</sup> The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, China

<sup>b</sup> Guangdong Provincial Hospital of Chinese Medicine, Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou, China

<sup>c</sup> Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou, China

<sup>d</sup> Chinese GRADE Center, Lanzhou, China

<sup>e</sup> WHO Collaborating Centre for Guideline Implementation and Knowledge Translation, Lanzhou, China

<sup>f</sup> Standardization Project Management Office of China Association of Traditional Chinese Medicine, Beijing, China

<sup>g</sup> The First Affiliated Hospital of Guangzhou Medical University, The First Clinical School of Guangzhou Medical University, Guangzhou, China

<sup>h</sup> Guangzhou Institute of Respiratory Disease, Guangzhou, China

<sup>i</sup> State Key Laboratory of Respiratory Disease, Guangzhou, China

<sup>j</sup> National Clinical Research Center for Respiratory Disease, Guangzhou, China

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## ABSTRACT

Influenza is a major public health problem worldwide. Mutations and resistance development make the use of antiviral therapy challenging. Chinese patent medicines are often used to treat influenza in China and well tolerable. However, the misuse of Chinese patent medicines is common. We therefore aimed to develop an evidence-based guideline on treating influenza with Chinese patent medicines in adults to guide clinical practice. We formed a steering committee, a consensus panel, a consultants' group and an evidence synthesis team to guide the development of the guideline. We formulated the clinical questions through two rounds of survey, and finally selected five questions. We then systematically searched the related evidence and conducted meta-analyses, evidence summaries and GRADE decision tables to draft the recommendations, which the consensus panel then voted on using the Delphi method. Finally, we formulated six recommendations based on the evidence synthesis and experts' consensus. For treating mild influenza, we suggest either Lianhua Qingwen capsule, Jinhua Qinggan granule, Banlangen granule, Shufeng Jiedu capsule, or Jinfang Baidu pill, depending on the manifestations. For severe influenza, or mild influenza in patients at high risk of developing severe influenza, we suggest Lianhua Qingwen capsule in combination with antiviral medications and supportive therapy. The strength of all recommendations was weak. Traditional Chinese medicine has great potential to help in the fight against influenza worldwide, but more high-quality studies are still needed to strengthen the evidence.

## 1. Introduction

Influenza is an acute respiratory infectious disease caused by influenza A or B virus [1]. An estimated 5%–10% of adults and 20%–30

% of children worldwide get influenza every year, causing annually about 290,000–650,000 deaths [1]. In recent years, both the incidence of influenza and the associated mortality have been rising. In 2018, the number of confirmed influenza cases and influenza related deaths in

**Abbreviations:** Acronyms, Glossary; AGREE, Appraisal of Guidelines for Research and Evaluation; AMSTAR, Assessing the Methodological Quality of Systematic Reviews; BLG, Banlangen; CI, Confidence interval; CPMs, Chinese patent medicines; GRADE, Grades of recommendations, assessment, development, and evaluation; IPGRP, International Practice Guidelines Registry Platform; IDSA, Infectious Disease Society of America; JHQG, Jinhua Qinggan; JFBD, Jinfang Baidu; LHQW, Lianhua Qingwen; MD, mean difference; NOS, Newcastle-Ottawa Scale; NHCPRC, National Health Commission of the People's Republic of China; PICO, Participants, intervention, comparison, outcome; RCT, Randomized control trial; RIGHT, Reporting Items for Practice Guidelines in Healthcare; RR, Relative risk; SFJD, Shufeng Jiedu; TCM, traditional Chinese medicines; WHO, World Health Organization

\* Corresponding author.

E-mail addresses: [dryiminli@vip.163.com](mailto:dryiminli@vip.163.com) (Y. Li), [drinlin620@163.com](mailto:drinlin620@163.com) (L. Lin).

<sup>1</sup> The authors contributed equally.

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China were 765,186 and 153, respectively [2]. In 2019, the number of influenza patients had reached 608,511 and deaths 143 already by the end of January [3]. Influenza can be treated with antiviral medication [4]. However, antiviral treatment has limitations: oseltamivir, the main antiviral agent used for influenza treatment, should be taken within 48 h of symptom onset to be effective [5]; the efficacy and safety of antivirals differ depending on the severity of symptoms and influenza strain [6]; and antivirals are challenging to manage as the viruses are mutating. As the use of antivirals has become more common, resistance has also increased: for example, in Europe up to 25 % of seasonal influenza A (H1N1) infections are resistant to oseltamivir [6]. The World Health Organization (WHO) downgraded oseltamivir on the list of essential medicines from a core drug to a complementary drug after reviewing the evidence [7]. Due to the severe burden of influenza worldwide, more treatment approaches and drugs are urgently needed.

In China, traditional Chinese medicine (TCM) has been used against influenza for thousands of years. A meta-analysis has reported that treatment by TCM leads to defervescence faster than antiviral therapy, and the duration of viral shedding is shorter in patients treated with integrated Chinese and Western medicine than in patients treated with antivirals alone [8]. Chinese patent medicines (CPMs) are herbal medicinal products developed according to the theory of TCM, which are manufactured in a ready-to-use form such as capsules, granule, pill or oral liquid.

Many types of CPMs are used to treat influenza. They are affordable and thus widely used in China. However, these medications are commonly misused, especially in Western-medicine based general hospitals [9]. In order to guide the clinical use of CPMs for influenza, improve their implementation and application, and promote the production of high-quality evidence, we developed this evidence-based guideline for the use of CPMs to treat influenza in adult patients [10].

## 2. Guideline development process

We developed this guideline following the methodology recommended by the 2014 WHO Handbook for guideline development [12] and using the AGREE II tool [11]. The final guideline was drafted according to Reporting Items for Practice Guidelines in Healthcare (RIGHT, <http://www.right-statement.org>) [12]. The whole guideline development process is shown in Fig. 1.

### 2.1. Sponsor and supporters

The China Association of Traditional Chinese Medicine initiated the development of this guideline. WHO Collaborating Centre for Guideline Implementation and Knowledge Translation and the Chinese GRADE Center / Evidence-Based Medicine Center of Lanzhou University provided methodological support.

### 2.2. Registration and protocol

This guideline has been registered on the International Practice Guidelines Registry Platform (IPGRP) [13] (registry number: IPGRP-2017CN028). The protocol can be obtained from IPGRP on request.

### 2.3. Scope

The guideline focuses on the use of CPMs to treat adult influenza patients. The primary target audience are general practitioners, respiratory medicine and emergency medicine clinicians, clinical pharmacologists, pharmacists in retail drug stores, and the general population. General internists and other health care professionals and policy makers involved in the management of influenza can also benefit from this guideline.

### 2.4. Group composition and meeting

The following four groups were formed to guide the development of this guideline:

- (1) Steering committee, consisting of two chief clinical experts and one chief methodological expert. The chief clinical experts, Lin Lin and Yimin Li, bore the ultimate responsibility for the development of the guideline. They made the final decisions at each stage of the guideline development, and led the writing of the final draft of the guideline [15]. The chief methodological expert, Yaolong Chen, was responsible for the top-level design of the guidelines, providing methodological guidance and training, and quality control throughout the entire process of developing the guideline [14].
- (2) Consensus panel, consisting of sixteen TCM specialists, two Western medicine specialists, and one clinical pharmacologist. The panel was responsible for determining the clinical questions, voting for recommendations, and building consensus [14]. The panel first conducted two rounds of Delphi survey through e-mail, to reach consensus on the recommendations to be included. Then they met in Beijing, China, on 13 November 2019, and voted on the wording of the recommendations. All members had filled in conflict of interest statement forms before they voted [15].
- (3) Consultants' group, consisting of seven TCM experts and seven Western medicine experts. They were consulted during the development of the guideline if necessary.
- (4) Evidence synthesis team, consisting of six participants. Two of the participants were evidence-based medicine researchers, two were clinicians, and two were students who had been trained in evidence-based medicine earlier. The team was responsible for the retrieval, evaluation, synthesis and grading of evidence, performing the systematic reviews, and formulating the summary of finding tables and recommendation decision tables [14].

### 2.5. Formulating questions

We conducted two rounds of questionnaire survey to frame the initial clinical questions. First, we sent questionnaires to 17 selected doctors, including chief physicians, attending doctors and resident doctors, who were asked to propose ten questions. After removing duplicates, a total of 64 questions were collected from the first-round questionnaire. Twenty-six questions were excluded because they were not in line with the objective, e.g. questions related to prevention of influenza, other diseases (common cold), influenza in children, and Tibetan medicine. Finally, 38 questions were included in the second-round questionnaire. The second-round questionnaire were sent to 200 doctors who were asked to rate the included questions and outcomes according to their importance. We received back the questionnaires from 106 respondents in 12 provinces or autonomous regions.

The results of the second-round questionnaire were ranked according to the mean importance score (1–5 points) of each question. After discussion by the steering committee, the four highest-ranking clinical questions were included: “How to treat mild adult influenza with CPMs?”; “How to treat severe adult influenza with CPMs?”; “How to use CPMs for pregnant and perinatal women with influenza?” and “How to treat elderly influenza patients with CPMs?” Other questions were all related to specific CPMs, so they were integrated into one question: “what is the effectiveness and safety of CPMs in the treatment of influenza in adults?” The evidence search for this question was not limited to the medications mentioned by the panel in the questionnaires. We also searched the evidence on all CPMs indicated for treating influenza in adult patients in the *National Basic Medical Insurance Drug List*, *National Essential Drug List*, and the *Chinese Pharmacopoeia* [16], as well as two drug electronic database (<http://ypk.39.net/>, <https://db.yaozh.com/>). The above questions all were formulated according to the Population, Intervention, Comparison,

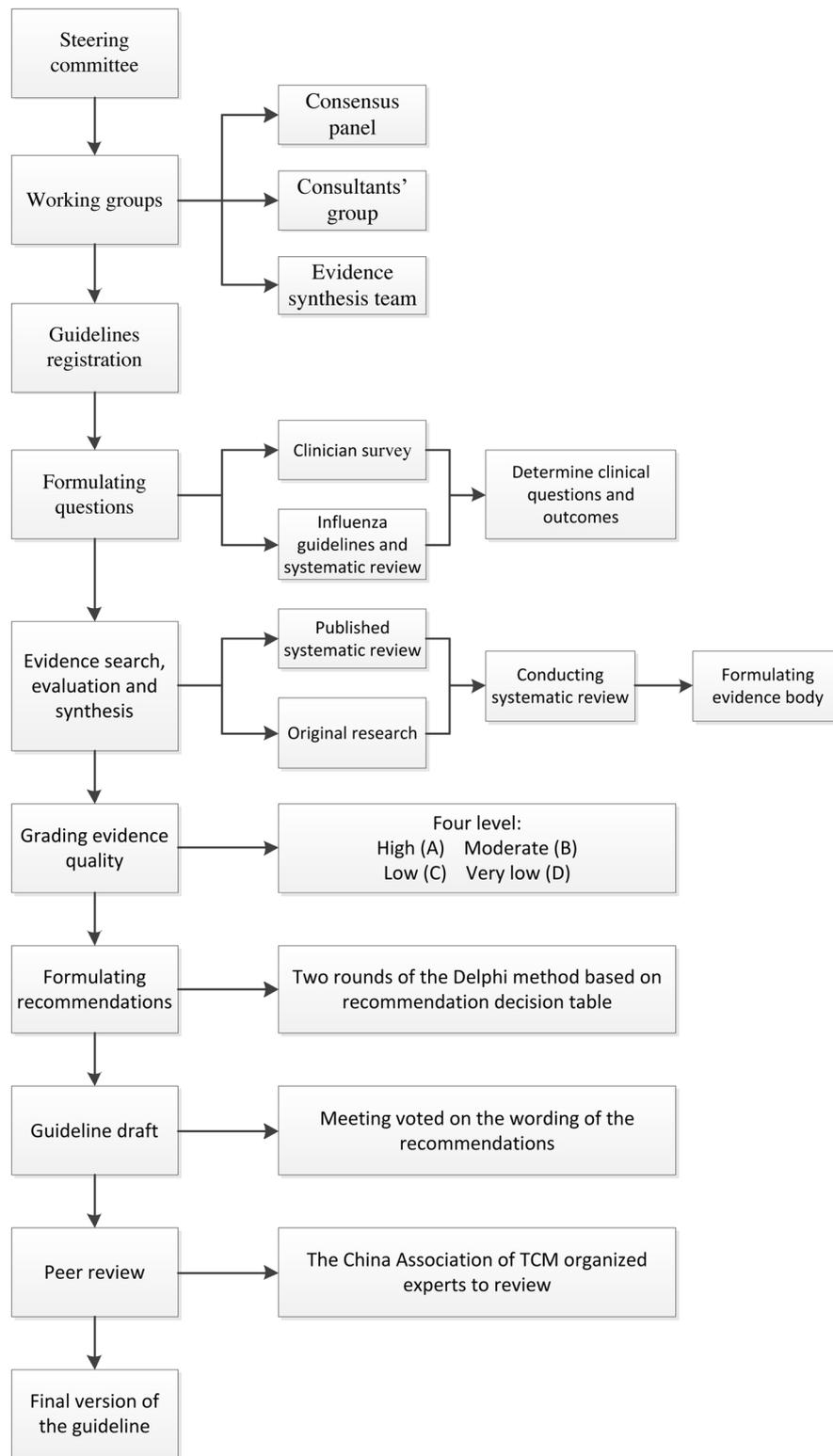


Fig. 1. Influenza guideline development process.

Outcomes (PICO) process [17].

### 2.6. Systematic review and grading

To answer the included clinical questions, we searched evidence and conducted systematic reviews for each question following the PICO framework. Three English-language and four Chinese-language databases were searched: MEDLINE, Embase, The Cochrane Library, CNKI,

SinoMed (CBM), Wanfang and VIP database. We included primarily systematic reviews, meta-analyses and randomized control trials (RCTs). Observational studies were also included if reviews or RCTs were not available. All databases were searched from their inception until April 30, 2019, and the languages were limited to Chinese and English. Two researchers independently extracted data and assessed the quality of studies. The search strategy was also peer reviewed by an external specialist [18].

**Table 1**  
Clinical recommendations.

No	Recommendation	Population	Intervention	Comparator	Outcomes	Strength of recommendation	Confidence*
1	LHQW capsule can be used to treat mild influenza that manifests with high fever, cough, thirst and bulbar conjunctiva hyperemia in adults	Adults with mild influenza	LHQW capsule	Oseltamivir	Time to defervescence, overall effectiveness, adverse events	Weak recommendation	Moderate
2	JHQG granule can be used to treat mild influenza that manifests with low to moderate fever, sore throat and cough, headache and myalgia in adults	Adults with mild influenza	MY (decoction of the JHQG granule)	Oseltamivir	Time to defervescence, overall effectiveness, adverse events	Weak recommendation	Low
3	BLG granule can be used to treat mild influenza that manifests with low to moderate fever, obvious throat swelling and pain, and cough, in adults	Adults with mild influenza	BLG granule + oseltamivir	Oseltamivir	Probability of fever resolution within 3 days, symptom relief, duration of hospitalization, adverse events	Weak recommendation	Low
4	SFJD capsule can be used to treat mild influenza that manifests with low to moderate fever, obvious cough and nasal obstruction, and sore throat, in adult patients	Adults with mild influenza	SFJD capsule	Oseltamivir	Overall effectiveness, pneumonia rate, adverse events	Weak recommendation	Low
5	JFBD pill can be used to treat mild influenza that manifests chill, fever, runny nose and myalgia in adults	Adults with mild influenza	JFBD (decoction of the JFBD pill)	None	Symptom alleviation	Weak recommendation	Very low
6	Severe influenza, and mild influenza in patients with high risk of progressing to severe influenza, can be treated with LHQW capsule combined with antiviral medication and supportive therapy	Adults with severe influenza	LHQW capsule + oseltamivir + supportive therapy	Oseltamivir + supportive therapy	Mortality, overall effectiveness	Weak recommendation	Low

Notes: Only the main PICO are listed in the table, complete information can be seen in the summary of the evidence in the main text.

\* Confidence is based on the quality of the evidence for main outcome.

The risk of bias in systematic reviews and meta-analyses was assessed by the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool [19,20], the risk of bias in RCTs using the Cochrane Collaboration tool [21], and the quality of observational studies by the Newcastle-Ottawa Scale (NOS) [22]. Disagreements were resolved by discussion or consultation with a third researcher. Meta-analyses of available studies were conducted using RevMan 5.3 (Cochrane Collaboration). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was applied to evaluate the quality of evidence and determine the strength of recommendations [23–25].

### 2.7. Formulating recommendations

In the GRADE process of grading evidence quality, five downgrading factors (study limitations/risk of bias, inconsistency of results, indirectness of evidence, imprecision, publication bias) and three upgrading factors (large effect, dose response, effect of plausible residual confounding) are considered [26]. The evidence synthesis team developed evidence summaries and a GRADE decision table to provide a clear description of benefits and harms. The certainty of the body of evidence was graded as high (Level A), moderate (Level B), low (Level C), or very low (Level D). When formulating recommendations, the consensus panel fully considered the magnitude of benefits and harms [27], the quality of evidence, resource implications and feasibility, and underlying patients' values and preferences. Then, the panel voted on each recommendation in two rounds of a slightly modified version of the Delphi method. Reaching a consensus required 75 % of votes. The strength of recommendations was graded as strong (Class 1) or weak (Class 2). We also referred to the syndrome differentiation and treatment rules according to the TCM principles when formulating the final recommendations.

### 3. Results

For the question “what is the effectiveness and safety of CPMs in the treatment of influenza in adults?”, we searched evidence on all CPMs that were indicated for treating influenza in the five included pharmaceutical sources described in Section 2.5. All CPMs included in this guideline have influenza indications in the drug instruction. Ninety-seven CPMs were obtained after removing duplicates. In addition, to enhance the clinical applicability, four CPMs recommended by a Chinese influenza guideline [28] (Shufeng Jiedu capsule, Sangju Ganmao tablet/granule, Yinhuang granule/capsule, Qingkailing oral liquid/capsule) and one CPM widely used by the public (Banlangen granule) were also included despite having no influenza indication in the drug instruction. Therefore, a total of 102 potentially eligible CPMs were assessed for effectiveness and safety. Three medications to treat pediatric influenza, 15 medications including Western medicine components and 10 Tibetan medicines were excluded. Among the remaining 74 medications, products consisting of the same ingredients but with different dosages or forms were combined. Finally, 37 CPMs were included in the search for evidence. We found relevant clinical studies only for 15 of these CPMs. For 10 CPMs we found either no statistically significant results when compared with the control group, or the effects were worse than in the control group (evidence profile can be shown in Appendix 3). Therefore, after weighing the advantages and disadvantages, the consensus panel did not make any recommendations for these 10 CPMs due to the insufficient clinical evidence. Finally, the consensus panel formed recommendations on the remaining five CPMs (the whole screening process of CPMs can be shown in Appendix 1). At the same time, after reviewing the composition of each type of CPMs and conducting meta-analyses on the efficacy and safety of each medicine on different TCM syndromes, we determined the most suited syndrome type for each included CPM.

For the remaining four clinical questions, only two questions (how

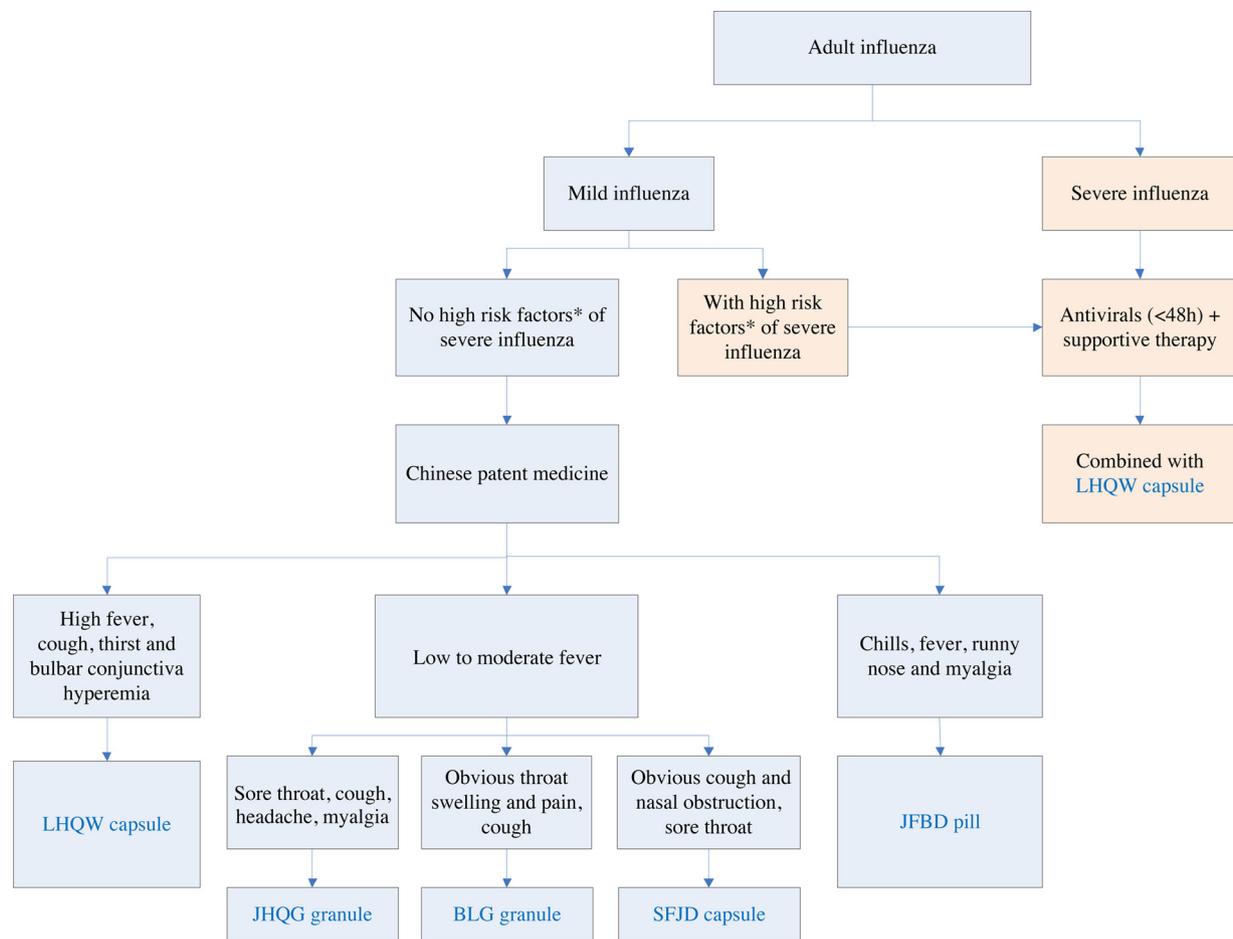


Fig. 2. Flow chart of treating influenza in adult patients with CPMs.

\*High risk factors of severe influenza [28]: 1) Adults aged  $\geq 65$  years; 2) Persons with chronic pulmonary, cardiovascular (except for hypertension), renal, hepatic, hematologic, neurologic and neuromuscular, metabolic disorders, tumor, immunosuppression; 3) Persons with obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>); 4) Pregnant and perinatal women.

to treat mild influenza in adult patients; and how to treat severe influenza in adult patients) could be answered with the existing evidence. The results for these two questions were integrated with those for the question “what is the effectiveness and safety of CPMs in the treatment of influenza in adults”. We found no evidence to answer the remaining two questions (how to use CPMs for pregnant and perinatal women with influenza; and how to treat elderly influenza patients with CPMs) we found no evidence to answer, so they cannot make recommendations. We finally made six recommendations for the effectiveness and safety of specific CPMs, including both mild and severe influenza (Table 1). The flow chart of treating influenza in adults with CPMs is shown in Fig. 2.

### 3.1. How to treat mild influenza in adults with CPMs?

Recommendation 1: Lianhua Qingwen (LHQW) capsule can be used to treat mild influenza that manifests with high fever, cough, thirst and bulbar conjunctiva hyperemia in adults (2B).

A relatively severe form of mild influenza, manifested by high fever, cough, thirst and bulbar conjunctiva hyperemia [28], is called a heat toxin attacking lung syndrome in TCM terminology. We suggest to treat adult patients with this syndrome with LHQW capsule.

#### 3.1.1. Summary of the evidence

We identified a total of 38 studies comparing LHQW capsule (either alone, or in combination with other treatment) with antivirals or other types of Chinese medicine. The course of treatment was 3–5 days. The

treatment was initiated within 48 h of symptom onset in 20 studies, and within 3–7 days in four studies. Fourteen studies did not report the timing. One of the studies included three groups: LHQW, oseltamivir and antipyretic analgesics [29], and we considered the results as two separate studies to facilitate the analysis. Therefore, we included a total of 39 studies. Eight RCTs [29–36] compared LHQW capsule versus oseltamivir for treating influenza in adults. LHQW capsule performed better than oseltamivir in terms of time to defervescence from treatment initiation (mean difference [MD] -2.54 h, 95 % confidence interval [CI] -5.02 to -0.07 h), and time from treatment initiation to end of each symptom, i.e. sore throat (MD -9.12 h, 95 %CI -12.01 to -6.23 h, cough (MD -10.23 h, 95 %CI -16.13 to -4.34 h and myalgia (MD -18.37 h, 95 %CI -35.11 to -1.63 h). There were no differences in overall effectiveness (defined as the proportion of patients who achieved at least 30 % reduction in symptom score after treatment [37]), the risk of headache or stuffy nose, or the duration of viral shedding between two groups.

Five RCTs [38–42] compared LHQW capsule combined with oseltamivir versus oseltamivir alone. The results showed that the time to defervescence was shorter with LHQW together with oseltamivir than with oseltamivir alone (MD -23.54 h, 95 %CI -45.05 to -2.03 h), but no difference was seen in overall effectiveness.

Twenty-six RCTs [29,43–67] compared LHQW capsule with ribavirin, antipyretic and analgesic drugs, or other CPMs. LHQW capsule showed superiority in the outcomes of overall effectiveness, duration of headache, duration of sore throat, duration of myalgia and time to defervescence (see Appendix 2).

Twenty-six of the above-mentioned 38 RCTs reported the risk of adverse events. Seven studies reported the rate of adverse events per group, which was lower in patients treated with LHQW capsule than oseltamivir (relative risk [RR] 0.29, 95 %CI 0.11 to 0.80) [29–32] [36], or ribavirin (RR 0.29, 95 %CI 0.11 to 0.80) [44,48]. Thirteen studies [30,43–45,57–60,62–66] reported no adverse events in the group receiving LHQW capsule. Six studies reported on a total of 13 cases of mild diarrhea, nausea or vomiting [31,35,38,46–48]; three studies [29,49,50] on 11 cases with tonsillitis, sinusitis or pneumonia; and one [36] study on one participant with dizziness in the groups receiving LHQW capsule. Three studies [32,39,51] did not describe the adverse events in detail.

Recommendation 2: Jinhua Qinggan (JHQG) granule can be used to treat mild influenza that manifests with low to moderate fever, sore throat and cough, headache and myalgia in adults (2C).

Mild influenza that is characterized with an early onset of symptoms, low to moderate fever, sore throat and cough, headache and myalgia, is one type of wind heat syndrome in TCM terminology. We suggest JHQG granule for adult patients with influenza with this type of manifestations.

### 3.1.2. Summary of the evidence

We conducted a meta-analysis of three RCTs [68–70] comparing JHQG granule versus placebo. Patients treated with JHQG granule had shorter time to defervescence (MD -15.11 h, 95 %CI -18.74 to -11.47 h) and higher overall effectiveness (defined in the same way as for LHQW; RR 1.09, 95 %CI 1.03–1.14) than patients in the placebo group. There was no difference between JHQG granule and placebo in the rate of viral shedding at end of treatment. JHQG granule originate from the Maxingshigan-Yinqiaosan (MY) TCM formula, and we therefore also considered evidence from studies on MY to treat influenza. Results of one trial [71] showed that fever resolved in patients taking MY together with oseltamivir sooner than in patients taking oseltamivir alone (MD -5.00 h, 95 %CI -9.61 to -0.39 h), and in patients treated with MY sooner than in untreated patients (MD -10.00 h, 95 %CI -14.74 to -5.26 h). There was however no difference between the arms with MY alone and oseltamivir alone. One trial [72] showed the time until fever resolution was longer when treated with JHQG granule than if treated with another CPMS, Ganmaoqingre Yin (MD -17.28 h, 95 %CI -25.29 to -9.27 h). The course of treatment was 3–5 days. In two studies treatment was started within 24 h, in two studies within 48 h, and in one study within 72 h of onset of influenza.

Three studies [68,69,71] reported on 13 participants taking JHQG granule or MY who experienced nausea, vomiting or diarrhea.

Recommendation 3: Banlangen (BLG) granule can be used to treat mild influenza that manifests with low to moderate fever, obvious throat swelling and pain, and cough, in adults (2C).

For patients with mild influenza manifesting with low to moderate fever, obvious throat swelling and pain, and cough (a type of wind heat syndrome in TCM terms), we also recommend BLG granule as a treatment.

### 3.1.3. Summary of the evidence

One trial [73] reported that BLG granule together with oseltamivir resulted in a lower risk of cough (RR 0.61, 95 %CI 0.43 to 0.87) and sore throat (RR 0.62, 95 %CI 0.42 to 0.91) and a shorter duration of hospitalization (MD -2.68 days, 95 %CI -3.74 to -1.62 days) than oseltamivir alone. However, there was no difference in the probability of fever resolution within three days of treatment initiation between the two groups. Another trial [74] showed the time to defervescence was shorter in patients treated with BLG granule than in patients treated with Bingduqing oral liquid, another CPMS (MD -5.30 days, 95 %CI -8.41 to -2.19 days). One trial [75] however showed BLG granule had a lower overall effectiveness than ribavirin injection (RR 0.68, 95 %CI 0.55 to 0.85). Another trial [76], comparing BLG granule and LHQW capsule treatment, both in combination with oseltamivir, found no

significant difference in the fever duration or symptom relief. All above studies treated the patients for 3–5 days, but did not report the timing of treatment initiation.

One trial [73] reported that two patients experienced nausea and vomiting, one patient diarrhea, one patient dizziness, and one patient rash after taking BLG granule together with oseltamivir. However, there was no difference in the risk of adverse events when compared with oseltamivir alone.

Recommendation 4: Shufeng Jiedu (SFJD) capsule can be used to treat mild influenza that manifests with low to moderate fever, obvious cough and nasal obstruction, and sore throat, in adult patients (2C).

For adult patients with mild influenza, manifesting low to moderate fever, obvious cough and nasal obstruction, and sore throat (one type of wind heat syndrome in TCM terms), we recommend SFJD capsule.

### 3.1.4. Summary of the evidence

Two trials [77,78] included influenza patients within 48 h of the onset of symptoms. They reported no differences in the overall effectiveness, or the risk of pneumonia, score of fever, chill, headache, body pain, running nose, sore throat, or cough between SFJD capsule and oseltamivir. The duration of treatment was 3 or 5 days. One trial<sup>79</sup> showed that SFJD capsule combined acyclovir had higher probability of fever resolution than acyclovir alone after three days treatment (RR 1.51, 95 %CI 1.21–1.90). There was no difference in the overall effectiveness or the probability of fever resolution within three days of treatment between SFJD capsule and acyclovir [79].

One trial [78] reported one patient experienced rash and two patients pneumonia after taking SFJD capsule. There was no difference in the risk of adverse events compared with oseltamivir.

Recommendation 5: Jinfang Baidu (JFBD) pill can be used to treat mild influenza that manifests chill, fever, runny nose and myalgia in adults (2D).

Some influenza patients manifest with serious chills, relatively mild fever, myalgia, and clear nasal discharge. This type of influenza is called wind cold syndrome in TCM terms. There exist only few CPMS that can be used against this type of influenza. We found only one case report about JFBD formula, which is the basis of the JFBD pill. We recommend JFBD pill in the treatment of the wind cold syndrome despite the very low quality of the supporting evidence.

### 3.1.5. Summary of the evidence

We found only one relevant case report with eight patients for this question. The study [80] included influenza patients who manifested fever and were treated by JFBD after 1–4 days of the onset of symptoms for a duration of 2–3 days. Results showed that the main symptoms disappeared and H1N1 virus nucleic acid turned negative after taking JFBD decoction for three days. No adverse events were reported.

## 3.2. How to treat severe influenza in adults with CPMS?

Recommendation 6: Severe influenza, and mild influenza in patients with high risk of progressing to severe influenza, can be treated with LHQW capsule combined with antiviral medication and supportive therapy (2C).

Severe influenza is defined as an influenza infection meeting any of the following conditions: 1. Persistent high fever for more than three days, accompanied by severe cough, blood sputum, or chest pain; 2. Rapid respiratory rate, dyspnea or cyanosis of the lips; 3. Mental abnormality: slow response, lethargy, restlessness; 4. Dehydration due to severe vomiting and diarrhea; 5. Pneumonia; 6. Obvious aggravation of the underlying diseases; 7. Other clinical conditions requiring hospitalization [28]. We suggest a combination of LHQW capsule with antiviral medication and supportive therapy to treat severe influenza. Although we found only limited evidence and the strength of the recommendation is weak, the prognosis of severe influenza is poor and thus this option should be considered.

### 3.2.1. Summary of the evidence

We found one study ( $n = 30$ ) [81] that compared LHQW capsule combined with oseltamivir versus oseltamivir alone for 5–7 days in patients with severe influenza. The study did not report the timing of treatment initiation. The combination therapy performed better than oseltamivir alone in terms of mortality (RR 0.20, 95 %CI 0.01–3.85) and overall effectiveness (RR 1.63, 95 %CI 0.97–2.72), but because of the small sample size the differences were not statistically significant. No adverse events were reported in the combination treatment group, while in the oseltamivir only group one patient experienced nausea and vomiting.

## 4. Discussion

WHO and the Infectious Disease Society of America (IDSA) have both published guidelines for the management of influenza [82,83], but neither of these included recommendations about Chinese medicine. National Health Commission of the People's Republic of China (NHCPRC) publishes the Guidelines of Influenza Diagnosis and Treatment every year. It currently recommends eight CPMs to treat mild influenza in adults [28]. Three of them were same as recommended by our guidelines: LHQW capsule, JHQG granule and SFJD capsule. NHCPRC guidelines include both Western medicine and TCM therapy. Their guidelines are based on authoritative experts' experience, and they have played an important role in the past attempts to fight against influenza in China. Our guideline is the first guideline of CPMs for influenza based on evidence from systematic reviews and applying the GRADE system to evaluate the quality of evidence. We believe our guideline will help to guide the future direction of research and treatment with CPMs for influenza. In addition, the cost of CPMs is likely to be low. A pharmaceutical economical study reported that the cost of SFJD capsule was lower than oseltamivir [84]. Another study compared the cost-effectiveness of four CPMs [85]. The results showed LHQW capsule is the most cost-effective treating plan for influenza.

This guideline is based on evidence from systematic reviews. However, the evidence was insufficient to answer some clinical questions formulated during the development process, such as how to use CPMs for pregnant and perinatal women or elderly people with influenza, and the effectiveness and safety of some specific CPMs for influenza. In addition, the quality of included studies was generally low. For wind cold syndrome of influenza, only one case report could be included. Meanwhile, some CPMs that are commonly used against influenza in clinic practice, such as Kangbingdu granule/oral liquid, Shuanghuanglian oral liquid and Chaihu oral liquid, are not included in the recommendations. This is because the instructions of some CPMs do not contain influenza indications despite being commonly used, or because of lacking or insufficient evidence to support the recommendation. It reflects the gap between current research and practice. Therefore, further high-quality studies are needed in the above fields. Another limitation of this guideline is that we did not search ongoing clinical trials. Potential publication bias may influence the results of the study.

## 5. Conclusion

We suggest five specific CPMs to treat mild influenza in adult patients, and a combination of a CPM with antiviral medication and supportive therapy for severe influenza. Although CPMs can only be used in China at present, a phase 2 LHQW capsule clinical trial is currently ongoing in the United States. CPMs may thus become more common also overseas in the coming years. Because of their effectiveness and relatively low cost, CPMs can help fighting influenza especially in developing or underdeveloped countries. The quality of studies of the studies we found on CPMs was however very low to moderate, so all of our recommendations were weak. More high-quality research on this topic is therefore needed to provide stronger evidence. Nevertheless,

CPMs are clearly a safe and effective alternative for influenza treatment, and the promotion of their use worldwide has great potential to help in the fight against influenza.

## Development groups

Steering committee: Lin Lin (clinical expert in TCM), Yimin Li (clinical expert in western medicine), Yaolong Chen (methodological expert).

Consensus panel: Lin Lin, Yimin Li, Hongchun Zhang, Zengtao Sun, Zhengping Bo, Suyun Li, Zegeng Li, Fengsen Li, Shanping Jiang, Bangjiang Fang, Yanping Zhang, Cuiling Feng, Shunan Zhang, Huiyong Zhang, Liangji Liu, Zhen Wang, Zhibin Chen, Yun Lu, Yini Luo.

Consultants group: TCM: Qing Miao, Yongjun Bian, Suofang Shi, Jia Zhu, Xiaoyan Gong, Yinji Xu, Hanrong Xue. Western medicine: Jiangtao Lin, Shaoxi Cai, Zifeng Yang, Huapeng Yu, Yubiao Guo, Ziwen Zhao, Jian Wang.

Evidence synthesis team: Lei Wu, Yanfang Ma, Yuanbin Chen, Nan Yang, Wenzhe Deng, Xufei Luo.

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## Declaration of Competing Interest

All members of the guideline panel reported no financial or intellectual conflicts of interest related to this guideline.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.phrs.2020.105101>.

## References

- [1] WHO, Influenza (Seasonal), (2019) [https://www.who.int/ith/diseases/influenza\\_seasonal/en/](https://www.who.int/ith/diseases/influenza_seasonal/en/).
- [2] PRC NHCCot, An Overview of Prevalence of Notifiable Diseases in China in 2018, (2018).
- [3] PRC NHCCot, An Overview of Prevalence of Notifiable Diseases in China in January 2019, (2019).
- [4] Prevention CfDca, Influenza Antiviral Medications: Summary for Clinicians, (2019) <http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm>.
- [5] A. Kumar, Early versus late oseltamivir treatment in severely ill patients with 2009 pandemic influenza A (H1N1): speed is life, *J. Antimicrob. Chemother.* 66 (5) (2011) 959–963.
- [6] A.E. Fiore, A. Fry, D. Shay, L. Gubareva, J.S. Bresee, T.M. Uyeki, Antiviral agents for the treatment and chemoprophylaxis of influenza — recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR Recomm. Rep.* 60 (1) (2011) 1–24.
- [7] Z. Kmietowicz, WHO downgrades oseltamivir on drugs list after reviewing evidence, *BMJ* 357 (2017) 2841 Clinical research ed.
- [8] J.H. Li, R.Q. Wang, W.J. Guo, J.H.S. Li, Efficacy and safety of traditional Chinese medicine for the treatment of influenza A (H1N1): a meta-analysis, *J. Chin. Med. Assoc.* 79 (5) (2016) 281–291.
- [9] Yh Wang, F. Meng, Xl. Li, Analysis of the Use of Chinese Patent Medicine in 6 Grade III-A Hospitals, *China Pharmacy* 22 (43) (2011) 4100–4102.
- [10] K. Yang, Y. Chen, Y. Li, H.J. Schunemann, Editorial: can China master the guideline challenge? *Health Res. Policy Syst.* 11 (2013) 1.

- [11] M.K.M. Brouwers, G.P. Brouman, et al., AGREE II: advancing guideline development, reporting and evaluation in health care, *J. Clin. Epidemiol.* 63 (12) (2010) 1308–1311.
- [12] Y. Chen, K. Yang, A. Marusic, et al., A reporting tool for practice guidelines in health care: the RIGHT statement, *Ann. Intern. Med.* 166 (2) (2017) 128–132.
- [13] International Practice Guideline Registry Platform, International Practice Guideline Registry Platform, (2019) Accessed 19, Dec <http://www.guidelines-registry.org/index.php?m=content&c=index&a=lists&catid=3&key=influenza>.
- [14] Y.L. Chen, Y.F. Ma, Q. Zhou, et al., Who Should Participate in the Development of Clinical Practice Guidelines? *Med. J. Peking Union Med. Coll. Hos.* 10 (5) (2019) 524–530.
- [15] X. Wang, Y. Chen, L. Yao, et al., Reporting of declarations and conflicts of interest in WHO guidelines can be further improved, *J. Clin. Epidemiol.* 98 (2018) 1–8.
- [16] C.P. Commission, Pharmacopoeia of the people's Republic of China, China Medical Science and Technology Press, 2015.
- [17] X. Huang, J. Lin, D. Demner-Fushman, Evaluation of PICO as a knowledge representation for clinical questions, AMIA Annual Symposium Proceedings AMIA Symposium (2006) 359–363.
- [18] L. Li, J. Tian, H. Tian, et al., Network meta-analyses could be improved by searching more sources and by involving a librarian, *J. Clin. Epidemiol.* 67 (9) (2014) 1001–1007.
- [19] B.J. Shea, J.M. Grimshaw, G.A. Wells, et al., Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews, *BMC Med. Res. Methodol.* 7 (2007) 10.
- [20] D. Pieper, R.B. Buechter, L. Li, B. Prediger, M. Eikermann, Systematic review found AMSTAR, but not R(evised)-AMSTAR, to have good measurement properties, *J. Clin. Epidemiol.* 68 (5) (2015) 574–583.
- [21] J.P. Higgins, D.G. Altman, P.C. Gøtzsche, et al., The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, *BMJ* 343 (2011) d5928.
- [22] G.A. Wells, B. Shea, D. O'Connell, et al., The Newcastle-ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses, (2019) [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).
- [23] G. Guyatt, A.D. Oxman, E.A. Akl, et al., GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables, *J. Clin. Epidemiol.* 64 (4) (2011) 383–394.
- [24] G.H. Guyatt, A.D. Oxman, R. Kunz, et al., Going from evidence to recommendations, *BMJ* 336 (7652) (2008) 1049–1051.
- [25] S.L. Norris, J.J. Meerpohl, E.A. Akl, et al., The skills and experience of GRADE methodologists can be assessed with a simple tool, *J. Clin. Epidemiol.* 79 (2016) 150–158 e1.
- [26] H. Balshem, M. Helfand, H.J. Schunemann, et al., GRADE guidelines: 3. Rating the quality of evidence, *J. Clin. Epidemiol.* 64 (4) (2011) 401–406.
- [27] J. Andrews, G. Guyatt, A.D. Oxman, et al., GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations, *J. Clin. Epidemiol.* 66 (7) (2013) 719–725.
- [28] China NHCotPsRo, Diagnosis and Treatment Programme of Influenza (2019), (2019) <http://guide.medlive.cn/guideline/19306>.
- [29] H.X. Ouyang, Q.Y. Tang, Y.Z. Chen, Y. Wei, G.S. Li, Clinical observation of Lianhuaqingwen department of emergency, capsules in treatment of the influenza A/H1N1, *China Med. Her.* 7 (30) (2010) 6–8.
- [30] Y.P. Ma, Y.L. Guo, L. Kang, L. Zhao, J. Peng, G.Y. Luo, Analysis of effectiveness of Chinese medicine on influenza A (H1N1), *Shanxi J. Trad. Chin. Med.* 31 (10) (2010) 1351–1353.
- [31] B.F. Li, C.Q. Zhang, M. Fu, W. Bai, B.H. Liu, S.S. Li, Clinical study of Lianhuaqingwen capsule in the treatment of influenza A (H1N1), *J. Med. Forum* 30 (23) (2009) 91–92.
- [32] Z.P. Duan, Z.H. Jia, J. Zhang, et al., Natural herbal medicine Lianhuaqingwen capsule anti-influenza A (H1N1) trial: a randomized, double blind, positive controlled clinical trial, *Chin. Med. J.* 124 (18) (2011) 2925–2933.
- [33] J.H. Li, M. Fu, Y.L. Li, Clinical observation and nursing of relieving clinical symptoms of influenza H1N1 with Lianhuaqingwen capsule, *Chin. J. Chin. Med.* 2 (5) (2010) 38–39.
- [34] G.X. Liu, J.Q. Yang, Z.Q. Gao, Y.X. Zhang, Y.C. Meng, A randomized controlled clinical study of Lianhuaqingwen capsule in the treatment of influenza A (H1N1), *Chin. Comm. Doc.* 29 (3) (2010) 12.
- [35] S.J. Wang, Study on the pharmacological mechanism of Lianhuaqingwen capsule against influenza virus, *Chin. J. of Clin. Rational Drug Use* 12 (05) (2019) 53–54.
- [36] L.Q. Chen, Observation on effectiveness of Lianhuaqingwen capsule on influenza, *J. Prac. Trad. Chin. Med.* 34 (10) (2018) 1265–1266.
- [37] N.M.P. Administration, Clinical Research Guidelines for New Drugs of Chinese Traditional Medicine on Influenza Treatment, (2016) <http://www.nmpa.gov.cn/WS04/CL2138/300218.html>.
- [38] X.J. Zhang, J. Li, Clinical study of Lianhuaqingwen capsule in the treatment of influenza A (H1N1), *J. China Pres. Drug* 14 (5) (2016) 91–92.
- [39] G. Li, Clinical effects of Lianhuaqingwen capsule combined with oseltamivir in the treatment of influenza, *Chin. J. Clin. Rational Drug Use* 9 (27) (2016) 137–138.
- [40] L.Y. Chen, Y.D. Wang, H. Huang, Clinical effects of Lianhuaqingwen Capsule on influenza virus, *Guansu Med. J.* 36 (8) (2017) 666–667.
- [41] F.L. Du, Analysis of the effects of oseltamivir combined with Lianhuaqingwen granule in the treatment of influenza A virus, *Cardio. Dis. Elec. J. Inte. Trad. Chin. West. Med.* 7 (15) (2019) 3.5.
- [42] X.K. Qian, Clinical effects of Lianhuaqingwen capsule combined with oseltamivir in the treatment of influenza, *Elec. J. Clin. Med. Lite.* 6 (48) (2019) 145–146.
- [43] L.B. Yang, Z.H. Ji, X.D. Gao, C.H. Gu, Phase II clinical study of Lianhuaqingwen capsule for influenza, *Trad. Chin. Drug Res. Clin. Pharm.* 16 (4) (2005) 290–293.
- [44] H.X. Luo, Clinical observation of 35 cases of Lianhuaqingwen capsule treated early stage of influenza, *Chin. J. Trad. Med. Sci. Technol.* 18 (6) (2011) 517–518.
- [45] B. Zhou, Observation on the effectiveness of Lianhuaqingwen capsule on influenza, *Chin. J. Misdia.* 11 (28) (2011) 6840.
- [46] C. Chen, Clinical effects of Lianhuaqingwen Capsule on influenza, *Mod. Diag. Treat.* 25 (2) (2014) 278–279.
- [47] X.G. Wang, X.J. Cui, X.S. Liu, H.X. Liu, Y.H. Li, Lianhuaqingwen capsules for influenza: observation of clinical efficacy, *China Pharmacy* 19 (27) (2008) 2146–2148.
- [48] X.F. Jin, Clinical observation on the treatment of influenza with Lianhuaqingwen capsule, *J. New Chin. Med.* 48 (6) (2016) 46–48.
- [49] M. Cui, X.Q. Pan, Lianhuaqingwen capsule in the treatment of 100 cases of influenza, *Zhejiang J. Trad. Chin. Med.* 46 (5) (2011) 333.
- [50] L.B. Yang, Z.H. Ji, B.Q. Wang, Observation on effectiveness of Lianhuaqingwen capsule on 280 cases of influenza, *Chin. J. Diff. Compli. Cases* 4 (5) (2005) 276–278.
- [51] B.F. Wang, Phase II clinical study of Lianhuaqingwen capsule in the treatment of influenza, *Chin. J. Health Care Nut.* 1 (26) (2016) 157.
- [52] Y.P. Wang, L.H. Yang, Z.X. Zuo, Lianhuaqingwen capsule in the treatment of 43 cases of influenza, *Chin. Med. Mod. Dis. Edu. China* 12 (12) (2014) 29–30.
- [53] X. Gao, Phase II clinical study of Lianhuaqingwen capsule in the treatment of 43 cases of influenza, *China Pharma.* 23 (22) (2014) 105–106.
- [54] Y.L. Yu, Y.X. Zhang, Observation on the effects of Lianhuaqingwen granule on the prevention and treatment of influenza, *Mod. J. Integ. Trad. Chin. Western Med.* 24 (10) (2015) 1121–1122.
- [55] N. Hou, Clinical effect of Lianhuaqingwen Capsule on influenza, *Special Health* 13 (2018) 250.
- [56] J. Liu, W.S. Ding, Z. Liu, Analysis of effectiveness of Lianhuaqingwen capsule on influenza, *Med. Diet. Heal* (11) (2018) 185.8.
- [57] T.H. Zhou, Observation on the symptom outcome of Lianhuaqingwen capsule in the treatment of influenza, *J. Psychol.* 14 (11) (2019) 2016.
- [58] L. Zhang, Effects of Lianhuaqingwen capsule in treatment of influenza, *Doctor (Z1)* (2018) 141.
- [59] L. Wang, Analysis on the experience of Lianhuaqingwen capsule in the treatment of influenza, *Health Awar.* 15 (2018) 259–260.
- [60] S.Y. Hu, Clinical study on Chaishi antipyretic granule in the treatment of influenza, *Chin. Comm. Doc.* 34 (4) (2018) 102–103.
- [61] C.C. Xiao, Clinical study of influenza, *Charming China* 3 (2019) 343–344.
- [62] L.Q. Chen, T.Y. Cai, 60 cases of influenza treated by syndrome differentiation, *J. Jiangxi Uni. TCM* 31 (01) (2019) 43–45.
- [63] X.B. Du, Q.H. Chen, Y. Xiao, An open-label, multi-center, random-control clinical study of Xiangju capsules in treatment of influenza, *China Med.* 14 (7) (2019) 981–983.
- [64] Y. Qing, Efficacy of Lianhuaqingwen capsule on influenza, *Healthc. Foodserv. Mag.* 13 (4) (2017) 62–63.
- [65] X.L. Liao, Clinical effects of Lianhuaqingwen capsule on influenza, *Contemporary Medicine* 23 (10) (2017) 120–122.
- [66] Y. Zou, T.H. Huang, Clinical effects of Lianhuaqingwen capsule on influenza, *J. Mod. Med. Health* 31 (4) (2015) 590–592.
- [67] J.H. Huang, Clinical observation on Lianhua Qingwen capsule in the treatment of influenza, *Chin. Comm. Doc.* 33 (08) (2017) 90–92.
- [68] G.Q. Li, J. Zhao, Z.T. Tu, et al., Treating influenza patients of wind-heat affecting lung syndrome by Jinhuaqinggan granule: a double-blinded randomized control trial, *Chin. J. Integ. Trad. West. Med.* 33 (12) (2013) 1631–1635.
- [69] J.P. Qi, X.Y. Qi, X.J. Wang, Clinical efficacy of different doses of Jinhuaqinggan granule on influenza and serum levels of cytokines, *Mod. Med. J.* 44 (12) (2016) 1664–1669.
- [70] G.Q. Li, Phase III clinical study, double-blinded, randomized control, Jinhuaqinggan granule for influenza with wind-heat affecting lung syndrome, Proceedings of 2013 Academic Annual Meeting of Chinese Association of Chinese Medicine; 2013 (2013) 228–239.
- [71] C. Wang, B. Cao, Q.Q. Liu, et al., Oseltamivir compared with the Chinese traditional therapy maxingshigan-yinqiaosan in the treatment of H1N1 influenza: a randomized trial, *Ann. Intern. Med.* 155 (4) (2011) 217–225.
- [72] J. Meng, B.R. Ni, L.Y. Yin, et al., Comparison of antipyretic effects of Ganmaotuire Yin and Jinhuaqinggan granules in treating influenza, *J. Tradit. Chin. Med.* 56 (05) (2015) 402–404.
- [73] B. Tu, W.M. Nie, P.P. Ding, et al., Efficacy of treatment of influenza A (H1N1) with oseltamivir phosphate and isatis root granules, *Med. J. Chin. People's Armed Police Forces* 24 (06) (2013) 465–467.70.
- [74] M. Li, Analysis of the clinical effects of Bingduqing oral liquid on influenza, *World Health Dig.* 06 (2014) 136–137.
- [75] K.F. Jiang, Clinical analysis of 100 cases of influenza treated with ribavirin injection, *China Foreign Med. Treat.* 27 (01) (2008) 25.
- [76] T.J. Jiang, Z.P. Zhou, J. Liu, et al., Efficacy of oseltamivir in the treatment of influenza A (H1N1), *Chin. Gen. Prac.* 13 (25) (2010) 2839–2841.
- [77] H.C. Li, X. Guan, L. Tian, et al., Economic evaluation of Shufengjiedu capsules versus oseltamivir capsules for adult patients with influenza-like illness, *Chin. J. New Dr* 26 (01) (2017) 14–21.
- [78] J. Niu, G.D. Li, Z.S. Wu, et al., Clinical observation of Shufengjiedu capsule in the treatment of 100 cases of seasonal influenza in Beijing, *Beijing J. Trad. Chin. Med.* 38 (03) (2019) 263–266.
- [79] Y.Y. Li, G.L. Tan, F.J. Zhu, Clinical study of Shufengjiedu capsule in the treatment of influenza, *J. Emer. Chin. Med.* 27 (10) (2018) 1734–1736.
- [80] Z.Q. Dou, 8 cases of influenza A H1N1 treated with Jingfangbaidu powder, *Infor. Trad. Chin. Med.* 28 (01) (2011) 67–68.
- [81] S.G. Sun, Analysis of 15 cases of severe influenza A (H1N1) treated by oseltamivir

- combined with Lianhuaqingwen capsule, *J. Guangxi Med. Uni.* 31 (4) (2014) 692–693.
- [82] WHO, Update: New Guidance on Clinical Management of Influenza Infections, (2018) [https://www.who.int/influenza/resources/documents/clinical\\_management\\_2012/en/](https://www.who.int/influenza/resources/documents/clinical_management_2012/en/).
- [83] T.M. Uyeki, H.H. Bernstein, J.S. Bradley, et al., Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza, *Clin. Infect. Dis.* 68 (6) (2019) e1–e47.
- [84] H.C. Li, X. Guan, L. Tian, et al., Economic evaluation of ShufengJiedu capsules versus oseltamivir phosphate capsules for adult patients with influenza-like illness, *Chin. J. New Drugs* 26 (1) (2017).
- [85] X.N. Kuang, Pharmacoeconomics analysis of four treatment regimens for influenza, *Chin. J. of Clin. Rational Drug Use* (2019) 22.