Study Protocol

Preventive effect of Lianhua Qingwen capsule on close contacts of seasonal influenza in residential environments: protocol for a multicenter, randomized, double-blind, placebo-controlled study

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Background: Seasonal influenza poses a high risk of death worldwide. Lianhua Qingwen (LHQW) is effective in shortening the time to symptom alleviation in patients with influenza, but there is a lack of convincing clinical trials targeting influenza prevention. This study aims to evaluate both efficacy and safety of LHQW in the preventing spread of seasonal influenza among close contacts under a cluster setting.

Methods: This study is a randomized, double-blind, multicenter clinical trial to evaluate the preventive efficacy and safety of LHQW in close contacts in a residential environments; 1,884 close contacts will be enrolled in this trial at 72 centers in China, with a five-day duration of LHQW or placebo. All participants were randomized into the LHQW and placebo groups in a 1:1 ratio via the interactive web response system (IWRS), balanced by the stochastic minimization method. Participants are required to undergo three visits (on days 3, 5, and 9 after initiation of medication). At each visit, a throat swab is collected from the participant, and RT-PCR is used to detect influenza virus nucleic acid. Symptom scoring will be performed nightly for the duration of the trial. The primary efficacy outcome was the secondary infection risk in close contacts on day 9 (±1) after medication. Safety outcomes are the incidence and severity of adverse events. This study used a randomized, double-blind, multicenter design method to evaluate the efficacy and safety of LHQW for close contacts in a congregate setting with risks of seasonal influenza transmission, to provide a valuable reference for clinical application. The treatment period of this study was five days and 1,884 close contacts were enrolled. All cases were randomized into experimental and placebo groups as index cases, and each subject returned three times during the treatment period on days 3, 5 and 9 after drug or placebo treatment, respectively, and the corresponding examinations were performed to evaluate the effect of the drug. Symptom scoring will be performed nightly for the duration of the trial.

Discussion: This trial is the first seasonal influenza prevention study of traditional Chinese medicines concerning prophylactic effects globally. Positive findings could demonstrate the efficacy of LHQW against seasonal influenza, which provides a new therapeutic option for infection prevention, symptom alleviation, cost reduction, and renewal of treatment guideline.

Trial Registration: The trial has been registered at Chinese Clinical Trial Registry (ChiCTR2300074385).

Keywords: Lianhua Qingwen (LHQW); clinical trial; influenza; preventive effect; residential environment

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Introduction

Seasonal epidemics and occasional outbreaks of human influenza viruses pose a heavy global burden of morbidity and mortality (1-3). Globally, there are an estimated one billion cases of influenza each year, of which three to five million are severe cases and 290,000–650,000 deaths are due to influenza-related respiratory disease (4). There are still many challenges to preventing influenza. Influenza vaccines have contributed to significant reductions in influenza morbidity and mortality. However, vaccines are currently limited by two main constraints: the continued antigenic evolution of influenza viruses, and the fact that vaccines are mainly produced using embryonated eggs, which limits the timetable and scale of their production worldwide (5). Antiviral drugs such as neuraminidase inhibitors (oseltamivir, zanamivir and so on) have been successfully used for influenza prevention in different scenarios. But side effects associated with oseltamivir, including nausea, vomiting, diarrhea, headache, and psychotic symptoms, limit the widespread use of these drugs to prevent influenza in the community (6,7). Meanwhile, a survey of anti-influenza drugs in the United States in 2022–2023 noted that 52.6% of districts reported local antiviral drug shortages, suggesting that there is a shortage of anti-influenza drugs during an influenza pandemic (8). Therefore, we still need other ways to deal with the growing epidemic of influenza.

Traditional Chinese medicine (TCM) is widely used for the prevention and treatment of influenza and influenza-like illnesses (9). Lianhua Qingwen (LHQW) is composed of 11 herbs, which has the effect of qing wen jie du (clear epidemic pathogenic factor and remove toxins), xuan fei xie re (disperse the lung and clear heat), and is mainly suitable for the treatment of influenza (10). A meta-analysis shows that LHQW can shorten the symptoms of influenza A, such as fever, cough, sore throat, and body aches, compared to oseltamivir, and has similar antiviral potency (11). Clinical practice guideline on treating influenza in adult patients with TCMs recommends LHQW for the treatment of influenza (12).

In vivo test, LHQW can inhibit the early infection of viruses in mice, including reducing the gene expression of interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), interferon-inducible protein-10 (IP-10) and monocyte chemoattractant protein-1 (MCP-1) caused by the virus (10). Mo *et al.* confirmed that LHQW can inhibit the influenza A H3N2 virus *in vitro* (13). Xu *et al.* proved that LHQW could effectively treat influenza A virus-infected pneumonia by intestinal microbiota analysis and network pharmacology, and its mechanism is associated with the regulation of the TLR4/NF-κB signalling pathway in the lungs by restoring intestinal microbiota and repairing the intestinal wall (14). A clinical trial demonstrated similar therapeutic efficacy for symptom duration between LHQW and oseltamivir (LHQW 69 hours *vs.* Oseltamivir 85 hours P>0.05), and no drug-related serious adverse events occurred in LHQW during the trial (15). Meanwhile, an *in vitro* assay demonstrated that prophylactic use of LHQW suppressed influenza A H3N2 virus (EC50 =0.031 g/mL) (13). Therefore, to understand the prophylactic effect of LHQW on influenza, a multicenter, randomized, double-blind, placebo-controlled study is designed to evaluate the efficacy and safety of LHQW in the prevention of seasonal influenza in close contacts in residential environments. We present the following article in accordance with the SPIRIT reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1542/rc).

Methods

The aim of this study is to evaluate the effectiveness, safety, and cost-effectiveness of LHQW in preventing seasonal influenza among close contacts in a clustered environment.

Study design

This is a randomized, double-blind, placebo controlled, multi-center trial to evaluate the efficacy of LHQW in the prevention of seasonal influenza in close contacts. The trial has been ongoing since November 02, 2023. We expect data collection to be completed by June 30, 2025. The findings will provide valuable information for clinical use. The study is expected to enroll 1,884 close-contact subjects

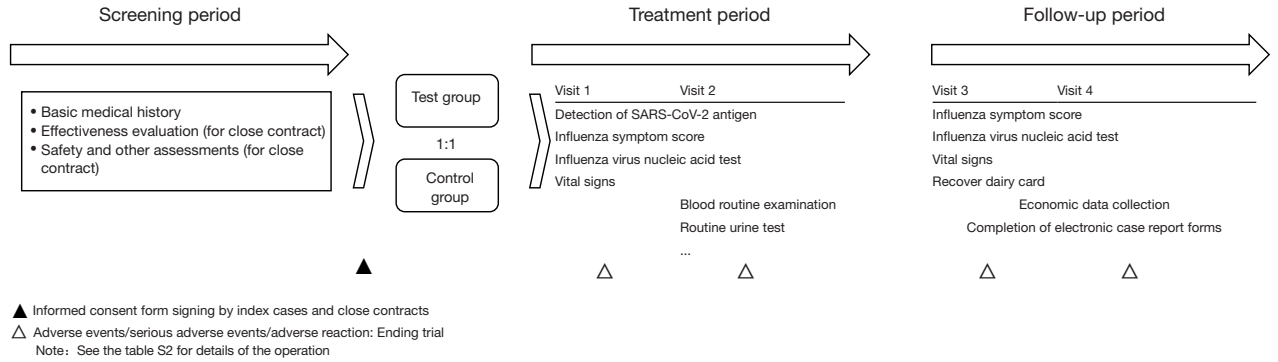

Figure 1 Flow chart. The study period consists of a screening period and a visit period, lasting a total of 30 days. Subjects will be randomly assigned to either the trial or control group after meeting the inclusion/exclusion criteria at screening. The screening window is 2 days, day 0 is the day of enrollment, and the day of drug initiation is "day 1", randomization and drug initiation can be on the same day, with a total of 5 days of dosing, and subjects will be visited on days the 3rd, 5th, and 9th after dosing to complete the relevant examinations, with a window of 1 day for the visit. Indicated cases were followed up by telephone on day five to document their co-administration of medication, with a follow-up window of one day. Close contacts were followed up by telephone on day 30 to collect economics data, with a follow-up window of 3 days.

and last for five days. All cases will be randomly assigned to either the test or control group as index cases. The subjects will receive three visits during treatment; on the 3rd, 5th, and 9th days after taking the drug, for corresponding examinations. Symptom scoring will be performed every night during the trial. The study flow chart is shown in *Figure 1*.

Endpoints

The primary efficacy endpoint is the secondary infection risk (SIR) of influenza among close contacts who take LHQW or placebo within nine days (±1 day) after randomization, i.e. the proportion of close contacts with secondary transmission of influenza, including symptomatic and asymptomatic subjects. Secondary transmission is inferred to be confirmed as influenza-positive by reverse transcription-polymerase chain reaction (RT-PCR) testing, and the virus subtype of any nasal or throat swab collected during the study period is consistent with the index case. Virologic detection methods are provided in Appendix 1. The Clopper-Pearson method will be used to calculate the 95% confidence interval (CI) and the Newcombe method will be used to calculate the rate difference between two groups and its 95% CI. The Pearson's χ^2 test or Fisher's exact test will be used for statistical tests.

Secondary efficacy endpoints include the following indicators within the study: (I) Proportion of infected clustered units in all clustered units on days the 3rd, 5th, and 9th (±1) after randomization. A clustered unit is considered infected when any close contact participating in this study tests positive for PCR. (II) Proportion of close contacts (both symptomatic and asymptomatic) who tested positive for PCR on days the 3rd, 5th, and 9th (±1) after randomization. (III) Proportion of close contacts (only symptomatic) who tested positive for PCR on days the 3rd, 5th, and 9th (±1) after randomization. The term 'symptomatic' refers to the presence of at least one symptom resembling influenza, with a score of ≥1 on the influenza symptom scale (*Table 1*). (IV) Comparison of mean scores for influenza-like symptoms when secondary transmission cases first appear. (V) The proportion of cases requiring additional influenza medication due to secondary transmission. All efficacy endpoints outcomes are summarised in the *Table 2*. Economic endpoints will be evaluated in the following: (I) quantification of the cost and effect of care; (II) evaluation of the variations in average costs and outcomes across different treatment groups; (III) assessment of the cost-effectiveness of therapies. The safety endpoints will include vital signs (body temperature, heart rate, respiration and blood pressure), clinical laboratory tests (routine blood and urine test, biochemical test of liver and kidney functions), electrocardiogram, and the frequencies and severity of adverse events.

Table 1 The scoring standard of clinical symptoms

Influenza symptom	Scoring criteria			
	0 (asymptomatic)	1 (mild)	2 (moderate)	3 (severe)
Fever	≤37.2 ℃	37.3–37.9 ℃	38.0–38.9 ℃	≥39 ℃
Headache	Asymptomatic	Occasional headache	Mild to severe	Severe headache, affecting the daily life and work
Sore muscles	Asymptomatic	Occasional muscle and joint pain	Mild to severe	Severe muscle and joint pain, affecting work and sleep
Aversion to cold	Asymptomatic	Slight aversion the cold	Aversion to cold, no relief after wearing more clothes	Chills
Runny nose	Asymptomatic	Occasional runny nose	Mild to severe	Frequent runny nose, affecting work and sleep
Fatigue	Asymptomatic	Mild fatigue, without affecting daily life and work	Mild to severe	Severe fatigue, affecting the daily life and work
Sore throat	Asymptomatic	Occasional sore throat	Mild to severe	Severe sore throat, affecting swallowing
Cough	Asymptomatic	Intermittent cough, without affecting daily life and work	Mild to severe	Frequent coughing day and night, affecting work and sleep
Nasal congestion	Asymptomatic	Unilateral nasal obstruction	Bilateral nasal obstruction	Bilateral nasal congestion, mouth breathing, affecting sleep

Inclusion and exclusion criteria

For this study, participants will be recruited through recruitment advertisements in hospital departments. Close contact residing with index cases in clustered units, such as co-living environments (including families, school dormitories, factory dormitories, and shared units), will be included (*Figure 2*). The inclusion criteria for close-contact are patients (I) living with the index cases who meet the inclusion criteria in the same clustered units, (II) aged 18 to 70 years, (III) whose result of rapid influenza virus antigen test is negative, (IV) without influenza-like symptoms within 1 week before randomization (the total score of flu-like symptoms is 0), (V) who are expected to live with the index cases for at least 7 days and be able to participate in visits as planned during nine days after randomization, (VI) who are willing to participate in this study and sign a written informed consent form (ICF). The exclusion criteria are detailed in *Table 3*. Participants who have completed the ICFs and have been deemed eligible for enrollment (i.e. assigned a random number) have the right to withdraw from the study and clinical trial at any time. The participants should be considered a drop-out/withdrawal case as shown in the Table S1. The stopping rule for this trial is as follows: (I) any serious safety event occurs; (II) the efficacy of the drug is too poor to be of clinical value; (III) there is a major error in the protocol that makes it difficult to evaluate the drug effect; or there is a major deviation in implementation that makes it difficult to evaluate the drug effect if the trial is continued; (IV) it is determined that the purpose of the study has been achieved and the sponsor or investigator believes that there is no need to continue the trial; (V) the sponsor requests discontinuation (e.g., for financial reasons, management reasons, etc.); (VI) the supervisory authority requests that the trial be withdrawn.

Randomization and blinding

The eligible index cases and their close contacts will be randomly assigned to the LHQW group or the placebo group at a ratio of 1:1 using the Interactive Web Response System (IWRS). This study adopts a double-blind design, where the investigators, subjects, clinical research associate (CRA), and clinical study coordinators remain blind. The investigational drugs and placebos are packaged in a unified manner to ensure no differences in appearance between them. And they are blinded according to the drug random

Table 2 Efficacy endpoints

Efficacy endpoints	Basic definition	Baseline	Calculation
Primary efficacy endpoints	The SIR of influenza of close contacts taking LHQW Capsules or placebo within nine days (±1 day) after randomization, i.e. the proportion of close contacts with secondary transmission of influenza[†], including symptomatic and asymptomatic subjects	Defined as the total number of close contacts in the cohort	SIR on Day 9 (±1) = number of close contacts with one positive result (+) of the influenza virus PCR assay within nine days (±1 day) after taking the medicines in the cohort/total number of close contacts in the cohort
Secondary efficacy endpoints	(I) The proportion of infected clustered units in all clustered units[‡] on days the 3rd, 5th, and 9th (±1) after randomization	Defined as the number of clustered units in the cohort	Proportion of infected clustered unit on Day N of treatment = number of infected clustered units on Day N of treatment on the cohort/number of clustered units in the cohort
	(II) The proportion of PCR (+) of all close contacts (sum of symptomatic and asymptomatic) at days 3, 5, 9 (±1) after randomization	Defined as the total number of close contacts in the cohort	Proportion of close contacts with positive PCR assay result (+) on Day N of treatment = number of close contacts with positive PCR assay result (+) on Day N of treatment in the cohort /total number of close contacts in the cohort
	(III) Proportion of (symptomatic)[§] close contacts with positive PCR assay result (+) on Days 3, 5, 9 (±1) after randomization	Defined as the total number of close contacts in the cohort	Proportion of (symptomatic) close contacts with positive PCR assay result (+) on Day N of treatment = number of symptomatic close contacts with positive PCR assay result (+) on Day N of treatment in the cohort/total number of close contacts in the cohort
	(IV) Comparison of the mean scores of influenza-like symptoms at the first appearance of secondary transmission cases	–	Mean value of the score for initial influenza-like symptoms in the cases of secondary transmission = total score for initial influenza-like symptoms in the cases of secondary transmission in the cohort/ total number of symptomatic cases of secondary transmission in the cohort
	(V) The proportion of cases of secondary transmission that require taking other drugs for influenza	–	Proportion of cases of secondary transmission requiring taking other medicines = number of cases of secondary transmission requiring taking other medicines = total number of symptomatic cases of secondary transmission in the cohort

[†], secondary transmission of influenza: secondary transmission is inferred to be confirmed as influenza-positive by RT-PCR testing and the virus subtype of any nasal swab or throat swab collected during the study period is consistent with the index case. [‡], infected Cluster: PCR (+) of any close contact participating in this study within the clustered unit, which is defined as an Infected Unit. [§], "symptomatic" is defined as the presence of at least one influenza-like symptom with an influenza symptom score of ≥1. LHQW, Lianhua Qingwen; RT-PCR, reverse transcription-polymerase chain reaction; PCR, polymerase chain reaction; SIR, secondary infection risk.

code table.

Quality control for different centers was carried out as follows: firstly, comprehensive standard operating procedures (SOPs) were formulated throughout the study, and the research teams of each center were trained separately and qualified before entering this trial, and each research center was equipped with qualified CRA and clinical research coordinator. The research teams operated in accordance with the SOPs throughout the study, and in case of protocol deviations (PDs) need to be A list of PDs was reported in accordance with the requirements of the drug clinical trial organization, and corrective

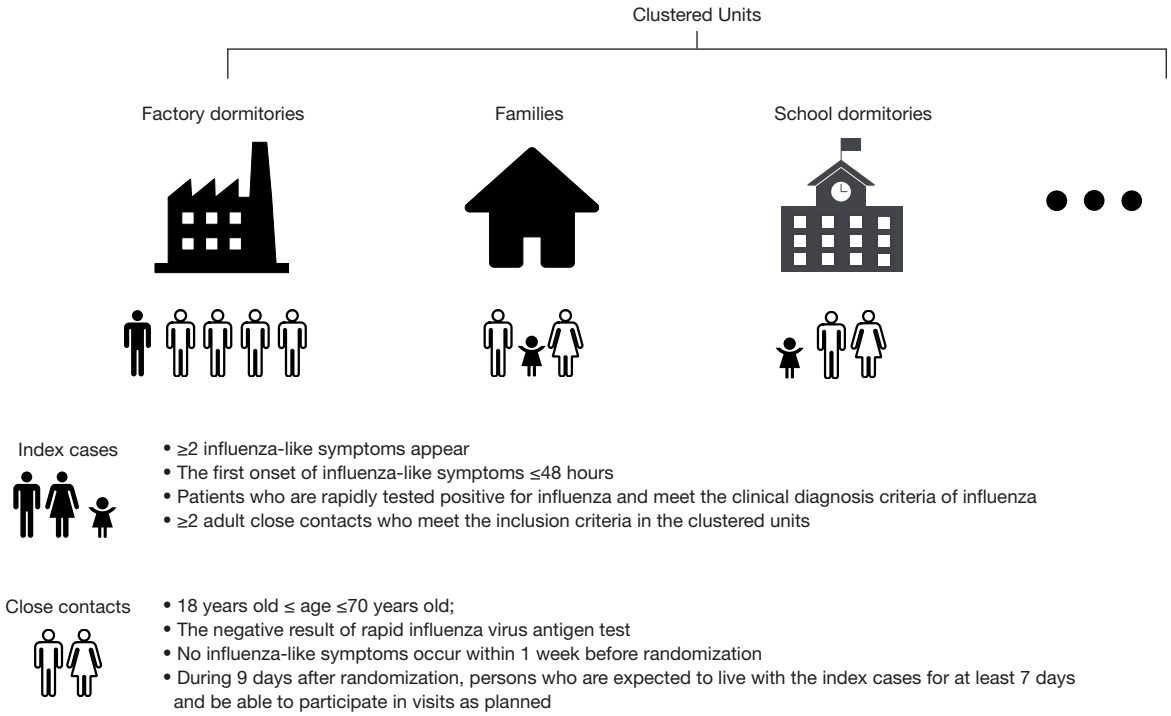

Figure 2 Inclusion criteria for indicated cases and close contacts. Clustered unit is defined as shared living environments, including the same family, the same school dormitory, the same factory dormitory, and the same shared unit, among others.

and preventive measures were developed. Secondly, the supervisors, the quality control staff of the drug clinical trial organization and the inspectors regularly quality control the centers, and the research team needs to correct the problems found and provide training if necessary. In addition, this study used an electronic data capture (EDC) system to collect clinical trial data, and the EDC system was configured with systematic logical verification and manual verification to question trial data that did not conform to the logic, and there were sub-center research teams to check and correct them one by one.

Intervention

Participants satisfying all criteria will be divided (1:1) randomly into two groups as follows: (I) LHQW group: four LHQW (0.35 g/per capsule) will be taken orally per time, three times daily, for five days. (II) Placebo group: Four placebo capsules (0.35 g/per capsule) will be taken orally per time, three times daily, for five days. The placebo contains only the same excipients (corn starch), and matches the LHQW in taste, color, dosage and directions for treatment.

The index cases receive standard clinical treatment without any interventions, with the medication used for treatment recorded in detail. Any drugs or therapies administered to close contacts due to comorbidities should be recorded in the case report form. This should include the drug (or other therapy) name, dosage, frequency, and time of usage for analysis and reporting in the summary. Before the onset of flu-like symptoms in close contacts, the following therapeutic drugs should not be used. (I) Antibacterial and antifungal drugs; (II) drugs with antipyretic effect; (III) drugs to improve flu-like symptoms. If a close contact develops flu-like symptoms, perform the following symptomatic treatment only after completing the influenza symptom score form on the same day. (I) If the close contact develops a fever with a body temperature continuously above 38.5 ℃ for more than four hours or above 39 ℃, oral non-glucocorticoid antipyretic drugs should be used. (II) If any close contact develops further flu-like symptoms, they may take medication to relieve flu symptoms (excluding TCM or Chinese patent medicine). It is crucial to record the date and time of each dose taken.

Table 3 Inclusion and exclusion criteria

Population	Inclusion criteria	Exclusion criteria
Index cases	(I) Gender and age are not limited	(I) The result of COVID-19 antigen test is positive
	(II) At least two of the following flu-like symptoms appear: fever, cough, nasal, congestion, sore throat, headache, runny nose and muscle or joint pain, and the symptom score is ≥1	(II) The close contacts in the clustered units who participated in this study but are tested positive for COVID-19
	(III) The first onset of influenza-like symptoms (a flu symptom score ≥1 point is judged as the onset of the symptom) within 48 hours	(III) Severe and critical patients who require hospitalization
	(IV) Patients who are rapidly tested positive for influenza and meet the clinical diagnosis criteria of influenza	(IV) Patients with other serious clinical conditions who require hospitalization or monitoring
	(V) In addition to the index cases, there are 2 or more adult close contacts who meet the inclusion criteria and do not meet the exclusion criteria in the clustered units*	(V) Other patients considered by the investigator to be inappropriate to participate in this study
	(VI) Volunteers who are willing to participate in this study and sign a written ICF	
Clustered close contacts	(I) The index cases in the same clustered units who meet the inclusion criteria and does not meet the exclusion criteria	(I) The result of rapid COVID-19 antigen test is positive
	(II) 18–70 years old	(II) Pregnant perinatal and nursing women
	(III) The result of rapid influenza virus antigen test is negative	(III) Patients combined with serious diseases of major organs or systems**
	(IV) No flu-like symptoms occur within 1 week before randomization (the total score of flu-like symptoms is 0)	(IV) ALT >5 ULN, AST >5 ULN or SCr >1.5 ULN in the screening results
	(V) During nine days after randomization, persons who are expected to live with the index cases for at least 7 days and be able to participate in visits as planned	(V) Persons who have taken Lianhua Qingwen preparation or any drugs with antiviral effect within 7 days***
	(VI) Volunteers who are willing to participate in this study and sign a written ICF	(VI) Persons who have been vaccinated against influenza within 6 months
		(VII) Persons who are allergic to the investigational drug
		(VIII) Patients who have participated in other drug clinical trials within 1 month prior to the screening test
		(IX) Other patients considered by the investigator to be inappropriate to participate in this study

*, clustered units refer to the co-living environments, including the same families, school dormitories, factory dormitories and shared units, etc. **, serious diseases of major organs or systems and hematopoietic system. Such as congestive cardiac failure, with severity levels of III to IV by NYHA classification; significant arrhythmias or abnormal heart valves that cause hemodynamic impairment; history of unstable angina or myocardial infarction within the past 6 months; malignant tumors in the non-radiotherapy or non-chemotherapy stable period; advanced stage of pulmonary tuberculosis; severe hypertension; diabetic complications such as diabetic ketoacidosis; immunodeficiency diseases such as HIV that have not achieved immune function reconstruction; autoimmune diseases such as systemic lupus erythematosus. ***, drugs with antiviral effect. Such as: Jinhua Qinggan, Qingkailing, Shufengjiedu, Yinqiaojiedu, Sangjuganmao, Banlangen, Yinhuang, oseltamivir, zanamivir and peramivir in any dosage form. ALT, glutamic pyruvic transaminase; AST, glutamic oxaloacetic transaminase; COVID-19, corona virus disease 2019; HIV, human immunodeficiency virus; ICF, informed consent form; NYHA, New York Heart Association; SCr, serum creatinine; ULN, upper limit of normal.

Data collection

In this study, the clinical trial EDC, medication diary cards and symptom score form are used. On the 3rd, 5th, and 9th days, participants will record their medication status and symptom after taking the drug by using the medication diary card and symptom score form (Table S2).

Staff training and clinical monitoring

The Sponsor and the testing facility shall establish their respective quality control and quality assurance systems. The Sponsor should confirm that the CRA who has the medical/pharmaceutical background and has received the GCP training is responsible for the monitoring of the clinical trials. The detailed requirements for the monitoring of the testing facility will be recorded in the Clinical Monitoring Plan (CMP). Any moderate or serious adverse events will be reported to the Ethics Committee and the pharmaceutical supervisory and administrative departments.

Statistical analysis

The primary objective of this study is to assess the risk of secondary influenza infection in close contacts of influenza who have taken LHQW or the placebo within nine days (±1 day) after randomization. According to the results of previous clinical studies, the secondary transmission rate of the placebo group is estimated to be 17%, and the experimental group to be 9%; α=0.025, 1–β=0.95, and the sample allocation ratio between the two groups is 1:1; according to the calculation by PASS (2021) software, the test group and the placebo group are expected to each include 527 cases (16,17). The enrollment in this study is based on the results of rapid influenza virus antigen test. Considering the false positive rate of index cases and the false negative rate of close contacts are estimated to be 30% in total, the sample size should be increased to 1,506 cases; plus the drop-out rate of 20%, the sample size should be further increased to 1,884 cases. Therefore, the test group and the placebo group are expected to each include 942 cases. In this study, subjects will be recruited by means of recruitment advertisements in hospital departments, including but not limited to, display stands, posters, electronic screen playback, etc.

In this study, intent-to-treat set (ITTS) includes all cases that express their intention to receive treatment, sign an informed consent form, and undergo randomization. Full analysis set (FAS) includes all cases that have signed informed consent forms and undergone randomization, received treatment, and obtained corresponding efficacy endpoint records. The baseline data analysis and validity analysis are mainly based on the FAS set analysis results. For cases where the entire treatment process is not observed in the FAS set, the last observation data is carried forward to the Last Observation Carry Forward (LOCF). Per-protocol set (PPS) is a subset of FAS, including all cases in the experiment who complete drug treatment according to the protocol, without significant deviation from the protocol, and complete all evaluation contents. The PPS population is the secondary population for efficacy evaluation in this test. Cases of premature dropout due to ineffectiveness should be included in the per protocol set. Safety set (SS) includes all cases with recorded safety indicators. The incidence of adverse reactions is based on the total number of SS cases as the denominator.

We use SAS9.4 statistical software for statistical analysis. All statistical inferences will use two-sided tests. $P<0.05$ will be set to indicate statistical significant, and two-sided 95% confidence interval will be used. Inclusion and completion will be summarized, and the number of participants in the FAS, PPS and SS. The distribution of participants and list the causes of participant loss at each point in each group should be described in a flow chat. Quantitative data will be displayed as mean, standard deviation, and confidence intervals. Qualitative data should be displayed as the number of each category and corresponding percentage. Details of the methodology of the statistical analysis are given in appendix available at https://cdn.amegroups.cn/static/public/jtd-24-1542-1.docx.

Ethics and dissemination

This clinical trial will be conducted in accordance with the Declaration of Helsinki (as revised in 2013) and good clinical practice (GCP) guidelines. The protocol has received ethical approval from the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (Approved No. of ethic committee: ES-2023-144-01; Guangzhou, China), and informed consent will be obtained from each participant prior to enrollment. The trial has been registered at Chinese Clinical Trial Registry (ChiCTR2300074385). If participants decide not to participate or not to proceed with the study, they can

withdraw their consent at any time without consequence. The study results will be disseminated in peer-reviewed journals and presented at international conferences. Data are available on reasonable request to the corresponding author. Authorship of articles will be determined by discussion within the research team, adhering to authorship guidelines.

Discussion

To the best of our knowledge, this trial is the first seasonal influenza prevention study of TCMs concerning prophylactic effects globally. This study will conduct a cost-effectiveness analysis based on a whole-of-society perspective, which comprehensively considered medical costs relevant or irrelevant to disease. It is expected that this study will demonstrate the efficacy of LHQW against seasonal influenza, which provides a new therapeutic option for infection prevention, symptom alleviation, cost release, and renew of treatment guideline.

Most popular drugs in clinical practice against influenza includes but not limits to following ones: neuraminidase inhibitors, cap-dependent endonuclease inhibitors, and various non-NA and polymerase-targeted inhibitors. Numerous studies prove that these drugs' efficacy against influenza (18-22). At the same time, other researches also reported their shortages such as severe side effects, and resistance acquisition (23,24). Due to the efficacy of LHQW in treating symptomatic clusters such as fever, cough, and runny nose, LHQW is widely accepted in clinical application in China recently for strong symptom alleviation and treatment duration shortening (25). All components of LHQW, with long history of clinical experience, are reported to have respiratory infection alleviation effect. This study aims to translate application of LHQW from experience relying to scientific evidence supporting. Concerning the high costs of clinically popular drugs, this trial aims to provide a more economic and replaceable option during influenza outbreaks that fully takes into account of the costs, side effects and resistance risk (26).

In conclusion, our trial represents the world's first study on the prophylactic effects of TCMs against seasonal influenza. Favorable results could showcase LHQW's effectiveness in combating seasonal influenza, offering a novel approach for prevention, symptom relief, cost savings, and guideline updates.

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None.

Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1542/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1542/coif). N.Z. serves as Editor-in-Chief of *Journal of Thoracic Disease*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This clinical trial will be conducted in accordance with the Declaration of Helsinki (as revised in 2013) and good clinical practice (GCP) guidelines. The protocol has received ethical approval from the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (Approved No. of ethic committee: ES-2023-144-01; Guangzhou, China), and informed consent will be obtained from each participant prior to enrollment.

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