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Clinical outcomes of influenza-like illness treated with Chinese herbal medicine: an observational study

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OBJECTIVE: To present and analyze treatments and clinical outcomes of Chinese patients with influenza-like illness.

METHODS: We conducted a multi-site observational study from December 2009 to April 2010. Patients with influenza-like illness from 45 hospitals were enrolled. Patients received Chinese herbal medicine (CHM), conventional treatments, or CHM plus conventional treatments (combination treatment) according to the guidelines for influenza A/H1N1 2009 in China. The primary outcomes were the time to alleviation of symptoms and the incidence of complications. The secondary outcomes were the time until becoming afebrile, incidence of severe illness, testing negative on an influenza A viral test, and total medical fees.

RESULTS: In total, 5967 patients were enrolled. The percentages of patients prescribed CHM alone, conventional treatment, and combination treatment were 27.8%, 5.1%, and 67.7%, respectively. There were no significant differences in the time to alleviation of symptoms, incidence of complications, time to becoming afebrile, or rate of severe illness among the CHM, conventional, and combination treatment groups. The rates of testing negative on the influenza virus A rapid test and H1N1 virus test were 90.3% and 76.3%, respectively. However, significant differences were found in the total medical fees among the three groups: CHM treatments were more economical than the other two treatments.

CONCLUSION: The efficacy of CHM for influenza-like illness was not different from that of conventional treatments, but it was more economical.
In 2009, a novel swine-origin influenza A (H1N1) virus rapidly spread from China to many countries around the world, prompting the World Health Organization (WHO) to declare a pandemic on 11 June 2009. The first case of H1N1 infection in China was reported on 9 May 2009. Since then, the number of cases has continuously increased. As of 31 March 2010, more than 127,000 laboratory-confirmed cases had been reported in 31 different provinces; this included 800 deaths. Symptomatic care and antiviral therapy are the main treatments for H1N1. The neuraminidase inhibitors oseltamivir and zanamivir have been recommended by the WHO for patients who have or are at high risk of developing severe or progressive clinical illness. However, there is growing evidence that neuraminidase inhibitors are resistant to influenza viruses. Chinese herbal medicine (CHM) has a long history of use in the treatment of infectious disease. CHM has its own theoretical system with many important scientific contributions, such as Shang Han Za Bing Lun and Wenbing Tiabian. CHM has been widely used for colds and influenza in clinical practice in China. At the time of the severe acute respiratory syndrome outbreak in 2003, studies revealed evidence of potential positive effects of CHM, providing valuable information regarding the treatment of influenza A. Moreover, during the early stages of the H1N1 outbreak, clinical practice outcomes indicated that CHM had the potential effect of alleviating symptoms and shortening the course of treatment. Therefore, CHM may be a promising alternative or complementary therapy for influenza. However, more concrete clinical evidence is needed to demonstrate its effectiveness.

The present study began in December 2009 in China and was supported by the Chinese government’s program on “Clinical research on H1N1 pandemic influenza treated with CHM.” The aim of the study was to determine how Chinese physicians treated patients with influenza-like illnesses in clinical practice and compare the effectiveness of different treatments for influenza.

METHODS

Study design and setting
This multi-site observational study was conducted during the H1N1 outbreaks in China from December 2009 to April 2010. The study was conducted in 45 hospitals (including Chinese medicine hospitals, general hospitals, and infectious disease hospitals) from 16 provinces in 6 different regions. The study was conducted under the supervision of the Guangdong Provincial Hospital of Chinese Medicine (GPHCM). All enrolled participants were observed and followed up during their disease course. All observations and follow-up ceased within 7 days of the end of treatment. The study was registered on 10 February 2010 in the Chinese Clinical Trial Registry (ChiCTR-OCH-10000780) (http://www.chictr.org.cn/).

Participants
All eligible participants were outpatients diagnosed with suspected influenza A, either clinically or based on laboratory tests in accordance with the guideline released by the Chinese Ministry of Health. However, patients diagnosed with severe influenza according to the 2009 Chinese Ministry of Health guidelines for H1N1 pandemics were excluded from the study. Participants were recruited from December 2009 to April 2010. The study was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from the patients or their parent (guardian) after being informed of all aspects relevant to the patient’s decision to participate. Individual participants remained anonymous during and after data collection. The study was approved by the Institutional Ethics Committee of the Guangdong Provincial Hospital of Chinese Medicine (Approval No. 2008GL-50).

Treatment
Physicians prescribed medication according to the patients’ conditions. The study did not control for the treatment prescribed. Physicians selected CHM or conventional treatments with reference to the guidelines released by the Chinese Ministry of Health. The different treatments are defined as follows. (a) CHM is a traditional medical practice in China with its own diagnosis system and treatment principles. It was defined as the use of decoctions or products of Chinese patent medicine at least three times over the course of the disease in this study. (b) Conventional treatment is a conventional medical practice based on Western medicine principles. In this study, it included symptomatic treatments (routine conventional treatments for relieving symptoms such as fever, coughing, and phlegm production), antiviral treatments (routine use of antiviral drugs such as oseltamivir for at least 3 d over the course of the disease), and antibiotics (included because we found that some doctors prescribed antibiotics for patients with influenza). (c) Combination treatments were defined in this study as CHM plus conventional treatments.

Outcomes
The primary outcomes included the time to alleviation...
of symptoms and the incidence of complications. The time until alleviation of symptoms was defined as the number of days between the date on which the patients visited the doctor (baseline date) and the date on which all main symptoms had been alleviated for > 24 h. The main symptoms included nasal congestion, sore throat, cough, myalgia, fatigue, and headache. A four-level scale was used to evaluate symptoms: none, mild, moderate, and severe. Possible complications included bronchitis, pneumonia, tonsillar abscess, and several other complications described in the WHO H1N1 guidelines. The secondary outcomes were as follows: (A) The time until becoming afebrile, defined as the number of hours between the time at which patients visited the doctor and the time at which their temperatures dropped below 37.3 °C for a period of > 24 h. (B) The incidence of severe illness due to influenza, characterized the following symptoms and signs: (a) high fever (> 39 °C) lasting for 3 d; (b) heavy coughing, purulent sputum, bloody sputum, or chest pain; (c) rapid breathing, difficult breathing, or cyanosis of the lips; (d) altered mental status, blunted responsiveness or sensibility, drowsiness, dysphoria, or convulsions; (e) severe vomiting or diarrhea or dehydration; (f) signs of pneumonia on imaging examinations; (g) rapid increase in myocardial enzymes, such as creatine phosphokinase (CK) or creatine kinase isoenzyme (CK-MB); or (h) aggravation of existing physical illnesses. (C) Negative result on the influenza A viral test. (D) Total medical fees, including medication fees and clinic fees.

**Data collection**

The patients’ demographic data, vaccination history, history of recent contact with patients with influenza, history of serious medical problems, medications, and treatment costs were all recorded, and influenza-like symptoms were assessed during the study. We also collected laboratory test results if available, such as vital signs, blood test results, urine test results, liver function test results, renal function test results, electrocardiogram findings, chest radiography findings, influenza virus A rapid test results, and influenza H1N1 virus test results. A pre-developed case report form was used to collect all data. Patients were required to record their symptoms, body temperature, and medication taken in daily diaries. Researchers followed up all patients via telephone calls and/or in-person interviews each day for a maximum of 7 d after treatment. The patients were withdrawn from the study if their condition became severe or they died of influenza or any other causes.

**Data management and statistical analyses**

All physicians from the various centers were trained before the study. An independent organization, the Guangdong International Clinical Research Center of Chinese Medicine, conducted data monitoring. The case report forms from all of the centers were delivered to GPHCM after being reviewed. Eight data entry operators were trained in double entry with EpiData V3.1 software (EpiData Association, Odense, Denmark). The database was locked after all data had been cleaned.

For sample size calculation, we assumed that the time to alleviation of symptoms (the main outcome) was 4.0 d for CHM treatment, 4.2 d for conventional treatment, and 4.2 d for combined treatments; the standard deviation was 2.2 according to the data from the pilot study. Using analysis of variance to compare the outcome between groups, a power of 0.8, and significance level of 0.05, we found that 5250 patients were needed in the study. PASS 11 software (NCSS, Kaysville, UT, USA) was used to calculate the sample size.

Missing data regarding symptoms and body temperature were replaced by last observation carried forward (LOCF). Participants, who had taken medicine and had undergone collection of outcome data at least once, were analyzed.

The PASW Statistics 17.0 software package (SPSS Inc., Chicago, IL, USA) and STATA software 13 (Stata Corp., College Station, TX, USA) were used for the statistical analysis. Either a t-test or the Mann-Whitney test was used to compare continuous variables in the two groups. One-way analysis of variance or the corresponding non-parametric Kruskal-Wallis test was used to compare continuous variables in more than two groups; the χ² test was used to compare categorical variables. To control for confounders in different groups, either a binary or ordinal logistic regression model was performed to compare the time to alleviation of symptoms, time until becoming afebrile (categorized as either >24 or <24 h), incidence of complications and severe illness, and probability of testing negative on the influenza A viral test between the groups. The baseline variables were selected as covariates in the multivariable regression model if the P-value was <0.20. Total medical fees were compared between the groups with a generalized linear model. For all final regression models, parameter estimates were adjusted for both confounding variables and for cluster sampling at the hospital level. A P-value of <0.05 was considered statistically significant in the final models.

**RESULTS**

**Patients’ characteristics at baseline and treatment**

During the influenza A/H1N1 outbreak from December 2009 to April 2010, 22 531 potentially eligible outpatients with influenza-like illness visited fever clinics or emergency rooms of 45 hospitals in 16 provinces of 6 regions of China. In total, 5967 patients were enrolled in the study after screening. Of these 5967 patients, 11 discontinued treatment immediately after prescription and 62 were lost to follow-up after the
first visit. Therefore, 73 patients were excluded from the analysis because of a lack of data to evaluate the treatment effectiveness. The final analysis included data from 5894 patients: 1,641 (27.8%) in the CHM group, 295 (5.1%) in the conventional treatment group, and 3958 (67.1%) in the combination treatment group. A flow chart of the study is shown in Figure 1. The number of eligible patients in each hospital ranged from 10 to 781, as shown in Figure 2.

The baseline characteristics of patients in the CHM group, conventional treatment group, and combination treatment group are shown in Table 1. CHM, both alone and in combination, was used more frequently than conventional treatment in patients with a history of serious medical problems. The mean age of the 5894 patients was 26.1 years. The mean body temperature at baseline was 38.3 °C. Only 146 (2.5%) patients had received an influenza vaccination before the study. The influenza virus A rapid test positive rate was 11.2% among the 4972 patients who took the test. All baseline variables except sex, diastolic blood pressure, influenza vaccination, sore throat, and coughing were unbalanced between the groups (P < 0.05).

One aim of the study was to collect data on how physicians treated patients with influenza A/H1N1. From Table 2, we can see that the percentage of patients prescribed CHM alone was 27.8%. A total of 5.1% were prescribed conventional treatments and 67.1% were prescribed combination treatments. We examined all treatment data in this study and calculated the frequency of CHM, symptomatic treatment, antiviral treatment, and their combinations (Table 2). The numbers of patients for whom at least one of the following medications was used were as follows: CHM: 5599 (95.0%), symptomatic treatment: 3522 (59.8%), antiviral treatment: 327 (5.5%), and antibiotic treatment: 1648 (28.0%). After evaluating the concomitant diseases of patients who had accepted antibiotic treatment, we found that only 160 patients needed antibiotics for infectious diseases. Therefore, irrational use of antibiotics for influenza may have occurred in 1488 (25.2%) patients. CHM combined with symptomatic treatment was the most common treatment, and nearly one-third of the patients (27.8%) received CHM treatment alone. The rates of use of CHM in Chinese medicine hospitals and non-Chinese medicine hospitals were 95.7% and 91.0%, respectively.

**Length of time until alleviation of symptoms**
The mean time until alleviation of symptoms was 4.2, 4.4, and 4.4 d, respectively, in the CHM group, conventional treatment group, and combination treatment group. Alleviation of symptoms primarily occurred before the fifth day, and the symptoms of only 612 patients (10.4% of 5894) did not disappear after that time. An ordinal logistic regression model was used to adjust for confounding factors and compare the effectiveness among the three treatment groups (Table 3).
The dependent variable was number of days (1-7) until the alleviation of symptoms after the start of treatment. As shown in Table 3, after adjusting for cluster effects, there were no statistically significant differences between the conventional treatment group and the other two groups. Additionally, the patients who had had an influenza vaccine, a history of recent contact with patients with influenza, cough, or a higher temperature needed more days to recover from all symptoms.

Incidence of complications
Complications occurred in 96 of 5894 patients (1.6%). Complications included pneumonia (42 cases, 0.7%), tonsillar abscess (36 cases, 0.6%), bronchitis (6 cases, 0.1%), urinary tract infection (6 cases, 0.1%), and bronchial pneumonia (2 cases, 0.03%). There was also one case (0.02%) of each of the following complications: bacterial infection, otitis media, sore throat, acute glomerulonephritis, and pulmonary tuberculosis. The incidence of complications (Table 4) was 1.1% (18/1641) in the CHM group, 0.7% (2/295) in the conventional treatment group, and 1.9% (76/3958) in the combination treatment group. Binary logistic regression analysis showed that there were no statistically significant differences among the three groups ($P > 0.05$) (results not shown).

Length of time until becoming afebrile
The mean time until becoming afebrile was 40.0, 42.0, and 39.8 h in the CHM group, conventional treatment group, and combination treatment group, respectively. Just over half (50.9%) of the 5894 patients became afebrile within 24 h of treatment. The results shown in Table 5 indicate that no significant difference was found between CHM (CHM group and combination treatment group) and conventional treatment.

Incidence of severe illness
Of the 5894 patients, severe influenza occurred in 19 (0.32%): 5 cases (0.30%) in the CHM group, 1 case (0.34%) in the conventional treatment group, and 13 cases (0.44%) in the combination treatment.
| Characteristic          | CHM (n=1641, 27.8%) | Conventional treatments (n=295, 5.1%) | Combination treatments (n=3958, 67.1%) | Total (n= 5894) | Missing data No. | P value |
|------------------------|---------------------|--------------------------------------|--------------------------------------|----------------|------------------|---------|
| Male (%)               | 48.9                | 52.9                                 | 51.5                                 | 50.9           | 0                | 0.165   |
| Age (years)            | 27.5±15.9           | 26.2±13.3                            | 25.6±13.2                            | 26.1±14.0      | 3                | 0.001   |
| Height (cm)            | 157.7±18.4          | 159.1±12.0                           | 160.4±17.3                           | 159.7±17.9     | 276              | 0.001   |
| Weight (kg)            | 52.7±15.8           | 55.9±16.7                            | 54.1±14.9                            | 53.8±15.3      | 291              | 0.001   |
| SBP (mm Hg)            | 115.0±14.4          | 112.9±11.1                           | 115.4±13.8                           | 115.1±13.9     | 359              | 0.018   |
| DBP (mm Hg)            | 73.1±9.1            | 72.5±7.4                             | 73.4±8.7                             | 73.3±8.8       | 359              | 0.214   |
| Pulse Rate (bpm)       | 91.6±15.0           | 95.8±13.6                            | 95.0±14.4                            | 94.1±14.6      | 127              | 0.001   |
| Respiration (times/min)| 20.5±8.6            | 22.4±13.3                            | 20.3±5.0                             | 20.3±6.8       | 105              | 0.001   |
| Temperature (°C)       | 38.0±0.6            | 38.3±0.7                             | 38.4±0.7                             | 38.3±0.7       | 15               | 0.001   |
| Disease duration (d)   | 1.2±1.6             | 1.5±1.4                              | 1.1±1.7                              | 1.2±1.6        | 7                | 0.001   |
| Flu vaccination [n (%)]| 37 (2.3)            | 5 (1.7)                              | 104 (2.6)                            | 146 (2.5)      | 21               | 0.485   |
| History of serious medical problems [n (%)] | 167 (10.2) | 13 (4.4) | 358 (9.0) | 538 (9.1) | 5 | 0.006 |
| Contact history [n (%)]| 130 (7.9)          | 45 (15.3)                             | 405 (10.3)                           | 580 (9.9)      | 8                | 0.001   |
| Influenza virus A rapid test [n (%)] | Negative 1274 (91.1) | 153 (85.5) | 2990 (88.1) | 4417 (88.8) | 922 | 0.003 |
|                        | Positive 124 (8.9)  | 26 (14.5)                             | 45 (11.9)                            | 555 (11.2)     |                 |         |
| H1N1 virus test [n (%)]| Negative 39 (67.2)  | 7 (33.3)                              | 57 (38.5)                            | 103 (45.4)     | 5667 | 0.001 |
|                        | Positive 19 (32.8)  | 14 (66.7)                             | 91 (61.5)                            | 124 (54.6)     |                 |         |
| Nasal congestion [n (%)]| No 766 (46.8)   | 1543 (52.2)                           | 2135 (54.0)                          | 3055 (51.9)    | 7                | 0.001   |
|                        | Mild 518 (31.6)     | 87 (29.5)                             | 1155 (29.2)                          | 1760 (29.9)    |                 |         |
|                        | Moderate 316 (19.3) | 46 (15.6)                             | 601 (15.2)                           | 963 (16.4)     |                 |         |
|                        | Severe 38 (2.3)     | 8 (2.7)                               | 63 (1.6)                             | 109 (1.9)      |                 |         |
| Sore throat [n (%)]    | No 543 (33.2)       | 72 (24.4)                             | 1312 (33.2)                          | 1927 (32.8)    | 12               | 0.062   |
|                        | Mild 551 (33.7)     | 109 (36.9)                            | 1176 (29.8)                          | 1836 (31.2)    |                 |         |
|                        | Moderate 426 (26.0) | 103 (34.9)                            | 1155 (29.2)                          | 1684 (28.6)    |                 |         |
|                        | Severe 117 (7.1)    | 11 (3.7)                              | 307 (7.8)                            | 435 (7.4)      |                 |         |
| Cough [n (%)]          | No 457 (27.9)       | 57 (19.3)                             | 1119 (28.3)                          | 1633 (27.8)    | 12               | 0.085   |
|                        | Mild 699 (42.7)     | 142 (48.1)                            | 1574 (39.8)                          | 2415 (41.1)    |                 |         |
|                        | Moderate 430 (26.3) | 92 (31.2)                             | 1094 (27.7)                          | 1616 (27.5)    |                 |         |
|                        | Severe 51 (3.1)     | 4 (1.4)                               | 163 (4.1)                            | 218 (3.7)      |                 |         |
| Myalgia [n (%)]        | No 632 (38.6)       | 111 (37.8)                            | 1198 (30.3)                          | 1941 (33.0)    | 10               | 0.001   |
|                        | Mild 497 (30.3)     | 134 (45.6)                            | 1298 (32.8)                          | 1929 (32.8)    |                 |         |
|                        | Moderate 411 (25.1) | 41 (13.9)                             | 1189 (30.1)                          | 1641 (27.9)    |                 |         |
|                        | Severe 98 (6.0)     | 8 (2.7)                               | 267 (6.8)                            | 373 (6.3)      |                 |         |
| Fatigue [n (%)]        | No 395 (24.1)       | 70 (23.8)                             | 661 (16.7)                           | 1126 (19.1)    | 8                | 0.001   |
|                        | Mild 729 (44.5)     | 161 (54.8)                            | 1874 (47.4)                          | 2764 (47.0)    |                 |         |
|                        | Moderate 414 (25.3) | 55 (18.7)                             | 1132 (28.6)                          | 1601 (27.2)    |                 |         |
|                        | Severe 100 (6.1)    | 8 (2.7)                               | 287 (7.3)                            | 395 (6.7)      |                 |         |
**Table 1 Baseline characteristics of patients in CHM group, conventional treatment group, and combination treatment group (continued)**

| Characteristics                      | CHM          | Conventional treatments | Combination treatments | Total | Missing data No. | P value |
|--------------------------------------|--------------|--------------------------|------------------------|-------|------------------|---------|
|                                      | (n=1641, 27.8%) | (n=295, 5.1%)            | (n=3958, 67.1%)        | (n= 5894) |                 |         |
| Headache [n (%)]                     | No           | 643 (39.3)               | 138 (46.8)             | 1258 (31.9) | 2039 (34.7) | 13 | 0.001 |
|                                      | Mild         | 563 (34.4)               | 105 (35.6)             | 1533 (38.8) | 2201 (37.4) |          |
|                                      | Moderate     | 370 (22.6)               | 42 (14.2)              | 976 (24.7)  | 1388 (23.6) |          |
|                                      | Severe       | 62 (3.8)                 | 10 (3.4)               | 181 (4.6)   | 253 (4.3)   |          |
| Total score of symptoms              | 5.9±2.8      | 5.6±2.7                  | 6.3±2.8                | 6.1±2.8    | 32               | 0.001  |
| Time until alleviation of symptoms   | 4.2±1.2      | 4.4±1.2                  | 4.4±1.3                | 4.3±1.3    |                  | 0.001  |
| Time until becoming afebrile         | 40.0±27.4    | 42.0±25.0                | 39.8±26.6              | 40.0±26.8  |                  | 0.006  |

Notes: CHM: Chinese herbal medicine; SBP: systolic blood pressure; DBP: diastolic blood pressure; SD: standard deviation. Total symptom score: A score of 0 (none), 1 (mild), 2 (moderate), or 3 (severe) was assigned to the six main symptoms (nasal congestion, sore throat, coughing, myalgia, fatigue, and headache). The total symptom score for each participant was obtained by summing the scores of each of these six symptoms.

**Table 2 Treatment patterns of 5894 patients**

| Group                        | Medication | Frequency | Percentage (n/5894) (%) |
|------------------------------|------------|-----------|-------------------------|
| CHM group                    | CHM        | 1641      | 27.8                    |
| Conventional treatment group | ST         | 133       | 2.3                     |
|                              | ST+ABT     | 71        | 1.2                     |
|                              | ST+AVR     | 17        | 0.3                     |
|                              | ST+AVR+ABT | 16        | 0.3                     |
|                              | Total      | 295       | 5.1                     |
| Combination treatment group  | CHM+ST     | 2288      | 38.8                    |
|                              | CHM+ST+ABT | 811       | 13.8                    |
|                              | CHM+ABT    | 591       | 10                      |
|                              | CHM+ST+AVR | 109       | 1.8                     |
|                              | CHM+ST+AVR+ABT | 77   | 1.3                     |
|                              | CHM+AVR    | 42        | 0.7                     |
|                              | CHM+AVR+ABT | 40    | 0.7                     |
|                              | Total      | 3958      | 67.1                    |

Notes: CHM: Chinese herbal medicine; ST: symptomatic treatment; AVR: antiviral treatment; ABT: antibiotic treatment.

**Table 3 Time until alleviation from symptoms by treatment group in the regression model**

| Factor                          | OR     | Linearized SE | P value | 95% CI for OR |
|---------------------------------|--------|---------------|---------|---------------|
|                                 |        |               |         | Lower         | Upper         |
| Conventional treatment group    |        |               |         |               |               |
| CHM                             | 0.80   | 0.16          | 0.27    | 0.54          | 1.19          |
| Combination treatment group     | 0.85   | 0.17          | 0.41    | 0.57          | 1.26          |
| Flu vaccination                  | 1.69   | 0.34          | 0.01    | 1.13          | 2.53          |
| History of serious medical problems | 1.20  | 0.15          | 0.16    | 0.93          | 1.54          |
| Contact history                  | 1.54   | 0.27          | 0.02    | 1.08          | 2.18          |
| Nasal congestion                 | 0.82   | 0.02          | 0.01    | 0.77          | 0.87          |
| Coughing                         | 1.25   | 0.06          | 0.01    | 1.14          | 1.37          |
| Temperature                      | 1.59   | 0.10          | 0.01    | 1.40          | 1.81          |

Notes: OR: odds ratio; SE: standard error; CI: confidence interval; CHM: Chinese herbal medicine.
group. Binary logistic regression analysis (Table 6) showed no statistical significance among the three groups.

**Rate of testing negative on influenza A laboratory test**

Only 175 patients who tested positive on the influenza virus A rapid test at baseline tested positive again on the fifth day after treatment. A total of 158 of these patients (90.3%) tested negative. Only 38 patients with confirmed H1N1 virus at baseline were retested after treatment, and 76.3% (29/38) of these patients tested negative after treatment. The proportion of missing data was so high for this outcome that we did not perform comparisons among the groups.

**Total medical fees**

The mean total medical fees in the study was ¥117.7 (18.1 USD): ¥72.5 in the CHM group, ¥123.0 in the conventional treatment group, and ¥135.9 in the combination treatment group. A general linear model was used to compare fees among the three groups. Both unadjusted and adjusted estimates differed significantly among the three groups. Sex, a history of serious medical problems, height, weight, systolic blood pressure, pulse rate, respiration, temperature, and total symptom score at baseline were adjusted for in the model because the fees were found to be statistically significant ($P < 0.05$) in the bivariate analysis by single-factor analysis. Table 7 shows that significant differences were found during the comparison of total medical fees among the three groups. The CHM treatments were more economical than the other two treatments.

**Adverse events**

In total, 46 cases of adverse events were reported among the 5,894 patients: 26 cases of diarrhea, 14 cases of vomiting, 2 cases of combined diarrhea and vomiting, 2 cases of allergic reaction, 1 case of syncope, and 1 case of tinnitus. The 46 cases included 37 mild and 9 moderate adverse events. Eight cases were in the CHM group and 38 were in the combination treatment group.

**Table 4 Incidence of complications in the CHM group, conventional treatment group, and combination treatment group**

| Group                  | $n$ | Cases with complications | Incidence of complications (%) | Total |
|------------------------|-----|--------------------------|--------------------------------|-------|
|                        |     | No | Yes |                             |       |
| CHM                    | 1641| 1616 | 18 | 1.1 | 1634 |
| Conventional treatment | 295 | 290 | 2  | 0.7 | 292  |
| Combination treatment  | 3958| 3859 | 76 | 1.9 | 3935 |
| Total                  | 5894| 5765 | 96 | 1.6 | 5861 |

Notes: $n$: number of cases; CHM: Chinese herbal medicine. Missing data: 33 cases (7 in CHM group, 3 in conventional treatment group, 23 in combination treatment group).

**Table 5 Whether patients became afebrile within 24 h by treatment group in the regression model**

| Factors                  | OR   | Linearized SE | $P$ value | 95% CI for OR |
|--------------------------|------|---------------|-----------|---------------|
| Conventional treatment   |      |               |           |               |
| CHM                      | 1.25 | 0.52          | 0.59      | 0.55, 2.87    |
| Combination treatment    | 1.48 | 0.60          | 0.34      | 0.65, 2.34    |
| Sex                      | 1.17 | 0.07          | 0.01      | 1.04, 1.32    |
| Height                   | 0.99 | 0.01          | 0.01      | 0.98, 1.00    |
| Coughing                 | 0.89 | 0.04          | 0.02      | 0.81, 0.98    |
| Fatigue                  | 1.00 | 0.04          | 0.92      | 0.91, 1.09    |
| Temperature              | 0.47 | 0.04          | 0.01      | 0.39, 0.56    |
| SBP                      | 1.01 | 0.01          | 0.01      | 1.00, 1.02    |

Notes: OR: odds ratio; SE: standard error; CI: confidence interval; CHM: Chinese herbal medicine; SBP: systolic blood pressure.

**Table 6 Incidence of severe illness by treatment group in the regression model**

| Factor                  | OR   | Linearized SE | $P$ value | 95% CI for OR |
|-------------------------|------|---------------|-----------|---------------|
| Conventional treatment  |      |               |           |               |
| CHM                     | 1.18 | 1.18          | 0.87      | 0.16, 8.84    |
| Combination treatment   | 0.79 | 0.77          | 0.81      | 0.11, 5.56    |
| Temperature             | 3.28 | 0.58          | 0.01      | 2.30, 4.67    |

Notes: OR: odds ratio; SE: standard error; CI: confidence interval; CHM: Chinese herbal medicine.
and effective than herbal medicine. It appeared to be more comprehensive in the treatment of symptoms, specifically fever. Western medicine was used more frequently than conventional treatments, especially for patients with severe symptoms. CHM, both alone and in combination with Western medicine, was used more frequently than conventional treatment in patients with a history of serious medical problems.

These findings differ from those of a study titled “Treatment of Influenza: Chinese Medicine vs. Western Medicine.” According to that study, patients with mild illness preferred Chinese traditional medicine for treatment of symptoms, specifically fever. Western Medicine was preferred by patients with complicated illnesses because it appeared to be more comprehensive and effective than herbal medicine. There was limited evidence to support this claim at that time, and the author arrived at this conclusion from clues based on the patients’ choices. Our study provides evidence based on data from the times at which traditional Chinese medicine was used and conventional treatments were resumed in clinical practice. In this study, no significant differences were found in the time to alleviation of symptoms, incidence of complications, time until becoming afebrile, or rate of severe illness among the CHM, conventional treatment, and combined treatment groups. However, significant differences were found in the total medical fees among the three groups; CHM treatments were more economical than the other two treatments. In recent years, several clinical studies of H1N1 have been performed to evaluate the efficacy of CHM. These have included studies on lianhuaqingwen capsules and maxingshi-gan-qingwen. These two forms of CHM demonstrated potential positive effects against H1N1. However, a systematic review determined that confirmative conclusions on the beneficial effects of Chinese herbs on H1N1 influenza could not be reached because of the lack of both a placebo-controlled trial and repeated intervention tests. Two other systematic reviews of CHM for influenza also showed that CHM has potentially positive effects in the treatment of influenza but that current evidence remains weak. Therefore, CHM has yet to show a clear advantage over conventional treatments in the treatment of influenza.

One strength of this study is that a large number of patients with influenza-like illness were enrolled during the 5-month outbreak of influenza A/H1N1 in China. Furthermore, the sample collected covered most regions of China. Another strength is that we had 80% power for the primary outcome, meaning that the negative results (no significant differences) were unlikely due to a small sample size or chance. The main limitation of this study is that it was an observational study without a control group. It was thus difficult to isolate the efficacy of the three treatments. The samples in the three groups were not randomized and were therefore uneven. Even if we had tried to adjust for possible confounders in the analysis, we might have overlooked several of them, thus biasing our results.

In conclusion, although CHM does not have a better effect on influenza than conventional treatments, it is more economical. These findings serve as an overview of treatments for influenza-like illness using CHM in China and provide a basis for future research on this topic. Future randomized controlled trials should be conducted to evaluate and confirm our findings.

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| Group                      | n  | Medical fee (RMB, ¥) | Marginal estimate (mean±SE) | 95% CI | P value |
|----------------------------|----|---------------------|-----------------------------|-------|---------|
| CHM                        | 1641 | 72.5±71.8          | 83.9±5.5                    | 73.1  | 94.7    | 0.001  |
| Conventional treatment     | 295  | 123.0±153.4        | 170.3±9.2                   | 152.2 | 188.3   |       |
| Combination treatment      | 3958 | 135.9±125.0        | 180.0±4.3                   | 152.0 | 188.2   |       |
| Total                      | 5894 | 117.7±1.5          |                             |       |         |       |

Notes: n: number of cases; SE: standard error; CI: confidence interval; CHM: Chinese herbal medicine. Adjusted by sex, history of serious medical problems, height, weight, systolic blood pressure, pulse rate, respiration, temperature, and total symptom score at baseline.
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