
Report A

A herbal formula for the prevention of transmission of SARS during the SARS epidemic in Hong Kong Special Administrative Region — a prospective cohort study

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Abstract. Traditional Chinese medicine (TCM) has a long history of being used to treat respiratory ailments. Many clinicians in China have used TCM to treat SARS patients with favourable outcomes as the symptoms of SARS closely resemble those of *wen bing* (feverish disease). The use of TCM for the treatment of respiratory illnesses in China has shown promise in the prevention of SARS particularly among high-risk groups SARS attack rates for two cohorts of health care workers from 11 hospitals in Hong Kong SAR, one using a herbal supplement for a 2-week period ($n = 1063$) and a control cohort comprising all health care workers who did not receive the supplement ($n = 36\ 111$) were compared prospectively. Changes in quality of life and influenza-like symptoms of the herbal supplement users were also examined at three time points. Results None of the health care workers who used the supplements subsequently contracted SARS as compared to 0.4% of the health care workers who did not use the supplements ($p = 0.014$). Improvements in influenza-like symptoms and quality of life measurements were seen among users of the herbal supplements. Fewer than 2% of supplement users reported adverse events and all such events were minor. The results of this pilot study suggest that use of the TCM preparation is a safe, efficacious and affordable SARS prevention measure. The simple, uniform formula might be considered to have violated the fundamental principles of treatment advocated by herbal experts in that only one formula was used. However, its efficacy supports the feasibility of using a uniform formula when facing an urgent need for broad prevention.

Introduction

The first outbreak of SARS occurred in the Prince of Wales Hospital in Hong Kong SAR in 12 March 2003; a total of 39 cases were reported (1). Health care workers were one of the groups most affected in this epidemic. As of June 2003, 338 (19.5%) of the 1755 confirmed or suspected cases of SARS reported in Hong Kong SAR had occurred in health care workers, and of these a total of six health care workers working in public hospitals had died of the disease (2).

The Centre for Disease Control and Prevention in China has classified SARS as a disease related to *wen bing* (meaning “feverish disease” in TCM), based on the close resemblance between the two illnesses. The Centre also advised health practitioners to refer to traditionally prescribed treatments and recommendations

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for *wen bing* in the treatment of SARS. It was reported that many SARS patients in China received a treatment regime of mainstream Western medicine supplemented with Chinese herbal medicine (3). A number of health practitioners have claimed that the combined treatments with Western and Chinese herbal medicine may have contributed to the relatively low mortality from SARS in China (4).

Chinese medicine has a favourable reputation and a long history of treating respiratory ailments that resemble influenza. In ancient China, such ailments and diseases were so prevalent that *wen bing* developed into a highly specialized and sophisticated branch of Chinese medicine that can be traced back 500 years to the late Ming Dynasty. According to the traditional precepts of *wen bing*, influenza-like diseases can be divided into four stages:

- ◆ development of fever;
- ◆ nasal symptoms;
- ◆ fever and chills (serious illness); and
- ◆ haemoptysis (4).

In Western medicine, the first two of the above-mentioned stages (fever and other mild symptoms) may be viewed as symptoms that usually subside even without treatment. The later stages may represent more unusual conditions when bronchitis and late pneumonia occur, possibly requiring hospitalization. There is no simple effective treatment for influenza in Western medicine. It has, however, long been noted that *wen bing* practitioners have had measurable success in controlling symptoms in the early stages, and are, thereby, presumably able to prevent the ailment from progressing to bronchitis and pneumonia. As SARS may be considered to be a viral infection related to influenza, the use of a *wen bing* formula for prevention and treatment during the early stages of illness shows great promise. Proven efficacy of this formula would have far-reaching implications for reducing the number of SARS cases.

The primary objective of the present study was to investigate the efficacy of a herbal formula in the prevention of transmission of SARS among health care workers in the hospitals in Hong Kong SAR, by comparing a cohort of herbal formula users with a control group of non-users. The secondary objectives included investigations of the differences among herbal supplement users in their quality of life and in the frequencies of self-reported influenza-like symptoms, as measured before they began to take the formula and at week 2 and week 4 after commencing intake, as well as to evaluate safety data related to the intake of the herbal formula.

Methods

The herbal formula

The formula was created by combining two herbal formulae that have commonly been used in the prevention and treatment of early-stage influenza-like symptoms. The first formula *sang ju yin* has been used widely in southern China (5). The second, *yu ping feng san*, has been popular in central and northern

China (6). Two ingredients noted in the modern herbal pharmacopoeia to have strong antiviral properties were added to the two formulae. The entire formula therefore consisted of 12 herbs: Folium Mori, Flos Chrysanthemi, Semen Armeniacae Amarum, Fructus Forsythiae, Herba Menthae, Radix Platycodonis, Radix Glycyrrhizae, Rhizoma Phragmitis, Radix Astragali, Radix Saposhnikoviae, Folium Isatidis and Radix Scutellariae. These herbs have been used traditionally for more than a thousand years and are considered safe for consumption because no noteworthy adverse effects have been recorded (5, 6).

The herbs were purchased from a reputable TCM supplier to ensure high quality, and the herbal preparation was manufactured according to standard good manufacturing practice (7). The ingredients were boiled to form a decoction which was subsequently freeze-dried into pellets that could be easily reconstituted into a tea-like drink.

Subjects and data collection methods

Volunteers who were health care workers working in 11 hospitals regulated by the Hong Kong Hospital Authority were recruited for the study. All these hospitals had been caring for SARS patients. Once informed consent had been obtained, the study subjects received 14 packets of the herbal supplement free of charge and were advised to consume the herbal drink every day for two weeks. All the health care workers recruited were free from SARS symptoms when they joined the study. Exclusion criteria included: serious illness, renal insufficiency and any history of hypersensitivity to Chinese medicine. The initiative was supported by the Hong Kong Hospital Authority. Ethical approval was obtained from the Clinical Research Ethics Committee of the Chinese University of Hong Kong. The volunteers also received three identical short questionnaires which were to be completed before commencing herbal supplement use, at the end of the 2-week period (week 2) during which the herbal supplement was taken and then, another 2 weeks after completing the treatment (week 4). The volunteers were instructed to return the three self-administered questionnaires to the research team by fax at the conclusion of the study. The herbal formula was distributed around mid-April 2003. In Hong Kong, the last SARS case was reported on 11 June 2003, and the last SARS case among health care workers was reported on 4 June 2003.

In order to achieve the primary research objective, a cohort study design was used in which a cohort using the herbal formula was compared with another control cohort that consisted of all other health care workers from the 11 participating hospitals, who did not use the herbal formula. The two cohorts were prospectively followed up to see whether any cohort members contracted SARS during the study period (17 April 2003 to 17 August 2003), by comparing the names of the herbal formula users against a registry of all SARS cases among health care workers in Hong Kong SAR maintained by the Hospital Authority. The attack rates of the two cohorts were compared statistically.

To achieve the secondary objectives, a "pre-post" study design was used. No control group was used, as the study was conducted at the peak of the SARS epidemic when the Hospital Authority wished to offer the herbal supplement to as many front-line workers as possible. A total of 2601 health care workers (out of a total of 16 437 working in these 11 hospitals) received the herbal supplement

and a total of 1063 (40.9%) returned completed questionnaires to the investigators.

Outcome measures

For the primary research objective, the outcome measure was whether the study subjects contracted the SARS virus between 17 April 2003 and 17 August 2003. The figures were cross-checked with the Hospital Authority's database on 17 August 2003 to determine whether any of the herbal supplement users had contracted SARS. In order to address the secondary objectives, the investigators measured quality of life, self-reported influenza-like symptoms and various indices of *wen bing*-related symptomatology that had been suggested by a panel of expert practitioners of Chinese medicine in the supplement users at the three time points. The mental health and vitality subscales of the Chinese version of the Short Form-36 (SF-36), which had been validated in Hong Kong SAR, were used in the study to measure two domains of quality of life (8). The list of influenza-like symptoms included fever, chills, muscle pain, headache and "heavy feeling", cough, fatigue, rigors and "hot feeling" (feverishness). Each of these symptoms was measured by a visual-analogue scale (with scores of 0-10). The list of TCM symptoms included: thick tongue sign (yes/no), sore and/or dry throat (yes/no), sleeping problems (yes/no), feeling "cold", "heat" or "humid"(yes/no). All adverse events were also recorded.

An understanding of the influenza-like symptoms and *wen bing* symptoms was considered necessary because these self-assessed symptoms in general might have been used by the health care workers as indicators of the possibility of having contracted SARS during the epidemic.

Statistical analysis

The difference in the attack rates of SARS between the cohort using the herbal supplement and the control cohort was tested by Fisher's exact test. Changes in the SF-36 mental health and vitality subscales and the influenza-like symptoms before and after the intake of the herbal supplement were tested for statistical significance by using a paired *t*-test and McNemar's test.

Table 1. Background characteristics of the herbal supplement users (n = 1063)

	No of subjects	Percentage
Age (years)		
20-30	184	17.3
31-40	366	34.4
41-50	377	35.5
51-60	135	12.7
> 60	1	0.1
Gender		
Female	829	78.0
Male	234	22.0
Occupation		
Nurse	485	45.6
Non-clinically trained support staff ^a	283	26.6
Physicians, allied health workers and others ^b	295	27.8
Location of work		
Accident and emergency unit	16	1.5
Intensive care unit	98	9.2
Infection ward	166	15.6
General ward	289	27.2
Orthopaedics and traumatology	48	4.5
Outpatient clinic	110	10.3
Administrative area	93	8.7
Other ^c	243	22.9
Hospital		
A	414	38.9
B	139	13.1
C	132	12.4
D	86	8.1
E	80	7.5
F	79	7.4
G	35	3.3
H	29	2.7
I	28	2.6
J	26	2.4
K	15	1.4

^aGeneral service assistant, health care assistant, ward assistant, manual worker, steward, operating theatre assistant and blood-taking assistant.

^bPhysician, dietitian, audiologist, radiographer, physiotherapist, occupational therapist, podiatrist, technician and research assistant.

^cPharmacy, endoscopy unit, electrodiagnostic unit, telemedicine unit, information technology office, laboratories, X-ray unit, occupational therapy department, physiotherapy department, radiology department, department of prosthetics and orthopaedics, central office, admission office, rehabilitation, transportation, canteen, mortuary, central sterile supply department and health information centre.

Results

Background characteristics

The background characteristics of the subjects are summarized in Table 1. The distributions of the three types of health care workers (nurses, non-clinically trained support staff, physicians/allied health workers and others) of the two cohorts were comparable (Table 2).

Table 2. Comparison of the job distribution of the two study cohorts

Job category	Supplement user cohort	Control cohort
Nurses	485 (45.6%)	19 228 (53.2%)
Non-clinically trained support staff	283 (26.6%)	7 235 (20.1%)
Physicians, allied health workers and others	295 (27.8%)	9 648 (26.7%)
Total	1063 (100%)	36 111 (100%)

Efficacy in SARS prevention

None of the 1063 herbal supplement users contracted SARS, whereas the attack rate in the control group was 0.4% (64 out of 15 374). The difference was statistically significant ($p = 0.014$, one-tailed t -test).

Mental health and vitality subscales

The means and standard deviations of the mental health and vitality (quality of life) scores at days 0, 14 and 28 are summarized in Table 3. It can be seen that the mental health of the subjects improved from day 0 to day 14 ($p < 0.001$), and remained more or less constant from day 14 to day 28 ($p = 0.284$); the difference between the scores on day 0 and day 28 was also statistically significant ($p < 0.001$). The vitality score also showed statistically significant improvements from day 0 to day 14 ($p < 0.001$) and from day 0 to day 28 ($p = 0.010$), although it decreased slightly from day 14 to day 28 ($p = 0.019$).

Table 3. Changes in Short Form-36 mental health and vitality quality of life subscales

Days	Mental health			Vitality		
	Mean	(SD)	Paired t -test p -value	Mean	(SD)	Paired t -test p -value
0	60.08	(9.89)		57.88	(11.89)	
14	62.14	(9.25)		59.15	(11.77)	
28	62.34	(9.38)		58.63	(11.92)	
0 - 14			< 0.001			< 0.001
14 - 28			0.284			0.019
0 - 28			< 0.001			0.010

SD, Standard deviation.

Table 4. Changes in visual-analogue scale scores referring to western medicine's "influenza-like" symptoms among herbal supplement users

Days	Chill symptoms			Rigor symptoms			Muscle symptoms			Headache and heaviness symptoms			Cough			Fatigue			Fever symptoms		
	Mean	SD	Paired <i>t</i> -test <i>p</i> -value	Mean	SD	Paired <i>t</i> -test <i>p</i> -value	Mean	SD	Paired <i>t</i> -test <i>p</i> -value	Mean	SD	Paired <i>t</i> -test <i>p</i> -value	Mean	SD	Paired <i>t</i> -test <i>p</i> -value	Mean	SD	Paired <i>t</i> -test <i>p</i> -value	Mean	SD	Paired <i>t</i> -test <i>p</i> -value
0	0.41	1.35	–	0.37	1.18	–	1.63	2.22	–	1.41	2.14	–	0.59	1.27	–	2.94	2.61	–	1.18	2.11	–
14	0.35	1.17	–	0.34	1.07	–	1.46	2.07	–	1.23	1.91	–	0.52	1.14	–	2.70	2.38	–	1.27	2.16	–
28	0.30	1.08	–	0.32	1.09	–	1.44	2.12	–	1.04	1.81	–	0.43	1.09	–	2.53	2.35	–	1.20	2.13	–
0-14			0.035			0.170			< 0.001			< 0.001			0.016			< 0.001			0.025
14-28			0.007			0.442			0.597			< 0.001			0.001			< 0.001			0.017
0-28			< 0.001			0.121			< 0.001			< 0.001			< 0.001			< 0.001			0.765

SD, standard deviation.

Influenza-like symptoms

The mean and standard deviations of the visual-analogue scales for various influenza-like symptoms are summarized in Table 4. It can be seen that subjects tended to have fewer symptoms on days 14 and 28 than on day 0 ($p < 0.05$), except for rigors (days 14 and 28; $p > 0.05$) and fever (day 28; $p > 0.05$). Continuous improvement from day 14 to day 28 occurred for the following symptoms: chills, cough, fatigue, headache and feelings of "heaviness" ($p < 0.05$), whereas the figures for changes in symptoms of rigors, muscle pain and feverishness on days 14 and 28 were not statistically significant ($p > 0.05$).

Traditional Chinese medicine symptoms related to *wen bing*

The percentages of subjects reporting symptoms related to *wen bing* are shown in Table 5. From day 0 to day 14 and from day 0 to day 28, it can be seen that each of the listed symptoms except the symptoms related to bowel habit and stool condition improved. The prevalence of sore/dry throat conditions decreased from 38.1% to 27.1%. The percentage of respondents feeling "humid" decreased from 48.4% to 37.3% ($p < 0.01$). Between day 14 and day 28, the prevalence of most symptoms continued to decrease, except for the symptoms related to irregular bowel habits and sleep.

Adverse events

Of the 1063 respondents, none reported serious adverse events and only 19 (1.8%) reported minor adverse events. These included diarrhoea, sore throat, dizziness and nausea. Of the respondents who reported adverse events, nine ceased using the supplements, three halved the dosage and the others continued to use the herbal formula as prescribed. The details of the adverse events reported are summarized in Table 6. It should be noted that the reported symptoms (e.g. dizziness and nausea), were rather non-specific, and might not have been related to the herbal drinks at all.

Table 5. Percentages of subjects having symptoms that are related to wen bing

Symptoms	Percentage			McNemar test <i>p</i> -value		
	Day 0	Day 14	Day 28	Day 0 vs Day 14	Day 14 vs 28	Day 0 vs Day 28
Thick tongue sign	47.3	42.9	40.5	< 0.001	0.008	< 0.001
Dry/sore throat condition	38.1	30.8	27.1	< 0.001	0.003	< 0.001
Irregular bowel habit	23.8	23.0	22.6	0.575	0.696	0.250
Loose/watery/hard stool condition	16.7	28.1	17.1	< 0.001	< 0.001	0.826
Not good/bad sleep condition	85.6	81.0	81.7	< 0.001	0.494	< 0.001
Feeling "cold"	19.8	16.0	14.6	< 0.001	0.044	< 0.001
Feeling "heat"	22.2	19.5	17.4	0.013	0.018	< 0.001
Feeling "humid"	48.4	39.9	37.3	< 0.001	0.028	< 0.001

Table 6. Details of adverse events reported by subjects taking supplement

Subject	Adverse event
1	Diarrhoea, headache, dizziness
2	Diarrhoea, headache, dizziness
3	Diarrhoea
4	Constipation, sore throat, cold sores
5	Diarrhoea, dizziness
6	Dizziness
7	Sore throat
8	Sore throat, fitful sleep with many dreams
9	Insomnia
10	Palpitations
11	Low-grade fever
12	Sore throat
13	Headache, nausea
14	Diarrhoea
15	Fever and sweating
16	Dizziness, nausea, shaking hands, bowel pain
17	Irregular menstruation
18	Malaise
19	Diarrhoea, stomach ache, allergic skin reaction

Discussion

To the authors' knowledge, this is the first study to explore the possibility of using TCM to prevent SARS in a high-risk population (i.e. health care workers). Despite the preliminary nature of this investigation, it has the strength of having used a prospective cohort design, and having used the actual SARS attack rates

as the primary outcome measure. A randomized controlled trial could not, however, be carried out at the time of the study (which was conducted during the middle of the SARS epidemic). During this time, health care workers in Hong Kong SAR were contracting SARS as a result of breakthrough transmissions (9). Due to heightened concern over SARS transmissions among health care workers, there was strong motivation to provide them all with the highest degree of protection against SARS infection. Hence, the random allocation of subjects to a control group was neither feasible nor desirable. Nevertheless, the job distribution of the two cohorts was comparable. The timing and settings of the study were also unique. The two cohorts were at a high risk of contracting SARS. The large number of nosocomial transmissions in Hong Kong SAR allowed such a comparison to be made.

The study results are encouraging and are compatible with the claim that TCM is an efficacious treatment for SARS (10). There is preliminary evidence that the herbal formula used in this study may have protective effects against the virus. Although serological tests were not conducted on asymptomatic health care workers in our study sample to confirm their SARS seronegativity, a recent seroprevalence survey identified no asymptomatic cases in the same population of health care workers (11), lending credence to the finding of differential attack rates between the two cohorts. The results of another study that documented an increase in the immune function which persisted for a 2-week period after cessation of supplement use among 37 SARS laboratory technicians using an identical herbal supplement treatment regime to the one in this study also provided evidence to support the potential efficacy of these supplements as a SARS-prevention measure (12). The quality-of-life data as well as the data collected on TCM and Western allopathic symptomatology, further support the beneficial effects of the herbal supplement to at-risk individuals.

Although the present study was an innovative one, using TCM to treat respiratory ailments is widespread in China. An unpublished study has reported that approximately 4% of the general population were likely to use TCM or complementary medicine for the purpose of SARS prevention in Hong Kong, SAR (Lau et al, unpublished data). Establishing the efficacy of TCM as a SARS prevention measure would be likely to result in a heightened demand for its use in Chinese populations around the world as well as in non-Chinese communities. Hence, the potential for using TCM as a SARS-preventive measure should not be underestimated.

Herbal formulas had also been reported to be effective in preventing diseases such as influenza, but few of the relevant studies were randomized clinical trials (13). The major limitation of the present study is that it was not a randomized study, for the reasons discussed above. There is, however, no indication that health care workers who were at lower risk of contracting SARS were more likely to volunteer to use the herbal supplement. In fact, it is expected that the reverse would be true, i.e. that those who were at higher risk would have a stronger motivation to use the herbal supplement. The direction of the participation bias should therefore not confound the results. The response rate was another limitation as only slightly more than 40% of those participants who received the herbal packets returned the completed questionnaires. By checking the SARS registry, the investigators confirmed that none of the 3160 health care workers who received the herbal supplement had contracted the virus. The 2097 non-

responders were then regarded as non-users in the statistical analysis, providing a conservative estimate of the difference in SARS prevalence between the two cohorts. This would mean that if some of the non-respondents who had actually used the herbal supplement as prescribed were moved from the control cohort to the herbal-supplement-user cohort, the actual difference in the SARS attack rates between the two cohorts should be even more marked. In the most extreme case, if all of the non-respondents were classified as supplement users, the attack rates for the supplement users and control group would be 0 and 0.46%, respectively (Fisher's exact test, $p < 0.001$). One other limitation of this study was that the absence of assessment of quality of life and symptoms in the control cohort makes interpretation of these results difficult, as other potential confounders may exist. The high consistency of the study results, however, suggests that the herbal supplement has real beneficial effects on symptom control and quality of life. Consumption of the herbal formula is apparently safe because only 1.8% of the subjects who used it reported adverse effects, and some of these may have been unrelated to the herbal drink.

Very few studies have compared the effectiveness of different measures for preventing SARS and none have examined the use of nutritional supplements in SARS prevention. As the herbal formula used in this study is safe and generally affordable (the cost is approximately US\$ 8.5 for a 2-week supply), it merits consideration as a SARS prevention option. Large-scale controlled trials on the prevention of influenza in different high-risk groups, such as health care workers and elderly residents of nursing homes may be warranted.

Experts on herbal treatments might disagree with the use of a single herbal formula because they would generally prepare specific preparations tailored to fit specific groups of individuals showing different patterns of physiological characteristics. However, with the huge demand for immediate responses during the recent epidemic, the need for an instantaneous supply of the preventive drink overwhelmed any other considerations. It was also the opinion of our herbal expert that for this wide preventive need, more generalization in the herbal formula could be allowed: the appropriateness of this strategy had been demonstrated by the efficacy of the single formula when facing an urgent need for broad prevention.

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